

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-023

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-023	Submission Date(s): July 27, 2007
Brand Name	Emend®
Generic Name	Fosaprepitant dimeglumine
Reviewer	PeiFan Bai, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Gastroenterology Products
Sponsor	Merck
Submission Type; Code	Resubmission
Formulation; Strength(s)	Injection (115 mg/10 ml)
Indication	Prevention of chemotherapy-induced nausea and vomiting (CINV)

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1 Executive Summary

The newly submitted individual blood pressure data showed that concomitant administration of fosaprepitant and diltiazem caused more episodes of blood pressure decrease of greater than 20 mmHg than diltiazem alone. In response to the consult sent by the GI division, the Division of Cardiovascular and Renal Products (DCRP) commented that "IV fosaprepitant acutely reduces blood pressure slightly and acutely potentiates the effects of diltiazem upon blood pressure." In summary, concomitant administration of fosaprepitant and diltiazem

may result in clinically significant consequences due to a greater blood pressure decrease beyond that caused by diltiazem alone.

1.1 Recommendation

From the Clinical Pharmacology perspective, there may be clinically significant consequences caused by coadministration of fosaprepitant and diltiazem. A cautionary language should be added to the label regarding coadministration of these two drugs. The application is acceptable provided that a mutually agreeable label language is reached between the sponsor and the Agency.

1.2 Phase IV Commitments

The sponsor has agreed to a phase IV commitment of submitting surveillance data regarding the effects of fosaprepitant on blood pressure.

1.3 Regulatory Background

The Agency had concerns about the effect of intravenous fosaprepitant on the blood pressure of hypertensive patients receiving diltiazem, based on the results of the drug-drug interaction study (study 011) submitted by the sponsor. The concern was that hypertensive patients who received a dose of 100-mg intravenous fosaprepitant and oral 120-mg of diltiazem 3 times a day had clinically meaningful further decreases in systolic blood pressure (-6.0 mmHg) beyond the decreases they experienced when taking diltiazem alone.

In the approvable letter, the FDA requested additional information regarding the drug interaction study with diltiazem as suggested by Dr Sue-Chih Lee (Office of Clinical Pharmacology) in her review. The following is adopted from her review. **"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 GI Division issued a consult request to DCRP on Nov 16, 2007 and received written comments from Thomas A. Marciniak, M.D. on Dec. 17, 2007. Dr. Marciniak concluded that the study was underpowered but suggestive that IV fosaprepitant acutely reduces blood pressure slightly and acutely potentiates the effects of diltiazem upon blood pressure.

1.4 Summary of the Drug Drug Interaction Study

The drug drug interaction study was reviewed by Dr Sue-Chih Lee, and the following data are adopted from her review.

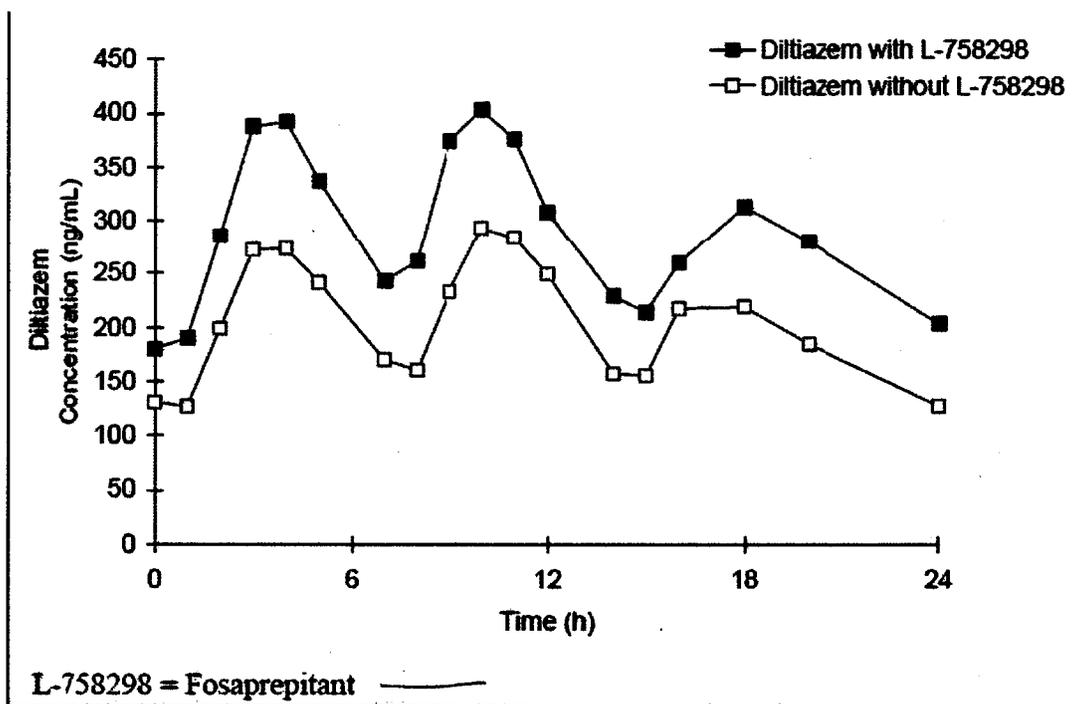


Figure : Mean (N=9) Plasma Concentration Profiles of Diltiazem During Administration of Diltiazem With Fosaprepitant or Placebo (Protocol 011)

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Table 1. Pharmacokinetic Parameters for Diltiazem Following Dosing of Diltiazem With and Without A Single Intravenous Dose of Fosaprepitant or Daily Oral Doses of Aprepitant

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	Geometric Mean		Geometric Mean Ratio (With/Without)	90% Confidence Interval	p-Value
	Diltiazem With Fosaprepitant [†]	Diltiazem Without Fosaprepitant [†]			
AUC _{0-24 hr} (ng•hr/mL)	6636.36	4752.19	1.40	(1.23, 1.58)	0.001
C _{max} (ng/mL)	422.81	289.36	1.46	(1.24, 1.72)	0.003
	Diltiazem With Aprepitant	Diltiazem Without Aprepitant			
AUC _{0-24 hr} (ng•hr/mL)	8496.53	5114.59	1.66	(1.44, 1.92)	<0.001
C _{max} (ng/mL)	472.49	306.58	1.54	(1.34, 1.77)	0.001

[†] After the first dose of diltiazem.

Table 2. Effect of Coadministration of IV Fosaprepitant on the Pharmacodynamic Parameters in Hypertensive Patients Receiving Oral Diltiazem

	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

For the effect of fosaprepitant on the pharmacokinetics of diltiazem, Dr. Lee concluded that "coadministration of single IV fosaprepitant 100 mg with oral diltiazem 120 mg increased AUC by ~40% for diltiazem, ~35% for desacetyldiltiazem, and ~11% for N-monodesmethyl-diltiazem compared to diltiazem administered alone. These effects are considered to be the result of CYP3A4 inhibition by aprepitant."

For the effect of fosaprepitant on blood pressure in hypertensive patients receiving diltiazem, Dr. Lee concluded that A single 100-mg IV dose of fosaprepitant when given with 120-mg oral doses of diltiazem administered 3 times daily resulted in a small but clinically meaningful decrease in diastolic blood pressure (-2.6 mmHg) and systolic blood pressure (-6.0 mmHg) beyond those changes induced by diltiazem alone. For a closer evaluation of the data, an information request will be made.

1.5 Review of Newly Submitted Individual Blood Pressure Data

Table 3 Frequency of blood pressure decrease of greater than 20mmHg between any two consecutive measurements of less than 20 minutes apart (Day 8)

Subject #	Diltiazem With Fosaprepitant	Diltiazem
1601		
1602*	✓	
1603		
1604		
1605		
1606		
1608		
1609		
1610		
1703		✓

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Data from individual listing of systolic blood pressure (mmHg) on Day 8 following diltiazem with and without fosaprepitant

* Data were missing between 2 to 2.5 hr post dose of diltiazem + fosaprepitant while the data from the same period for diltiazem alone were not.

Summary: The data above showed that subjects experienced more episodes of greater than 20 mmHg decrease in blood pressure between two consecutive measurements of less than 20 minutes apart when taking diltiazem and fosaprepitant concurrently than when taking diltiazem alone.

Eight subjects experienced greater than 20 mmHg blood pressure decrease when diltiazem was coadministered with fosaprepitant while only 5 subjects experienced such blood pressure decrease when diltiazem was administered alone.

1.6 Comments from the Consult to Division of Cardiovascular and Renal Products (DCRP)

DCRP judged the small study to be underpowered but suggestive that fosaprepitant acutely decreases blood pressure modestly. DCRP recommends that a post-marketing commitment be considered for better characterization of the effects of fosaprepitant upon blood pressure.

Reviewer's comments:

The individual subjects' data showed that co-administration of diltiazem and fosaprepitant caused further decrease in blood pressure beyond that caused by diltiazem alone. The time courses of blood pressure measurement and aprepitant plasma concentrations only shared a few common time points. The sporadic same time points between the PK and PD measurements do not render a concrete support for making a correlation between the plasma concentration of aprepitant and the extent of blood pressure further decrease.

The data in the table listed above showed that subjects experienced more episodes of greater than 20 mmHg decrease in blood pressure decrease when

taking diltiazem and fosaprepitant concurrently than when taking diltiazem alone.

A sudden decrease in blood pressure can be dangerous. For example, a decrease of 20mmHg (from 130 systolic to 110 systolic) can cause dizziness and fainting due to the brain failing to receive adequate blood supply. (<http://www.mayoclinic.com/health/low-blood-pressure>).

In its response to the consult issued by the GI Division, DCRP suggested that "IV fosaprepitant acutely reduces blood pressure slightly and acutely potentiates the effects of diltiazem upon blood pressure."

Based on the consult and my own review, co-administration of fosaprepitant and diltiazem may cause acute potentiation of the effect of diltiazem and result in clinically significant decreases in blood pressure beyond that caused by diltiazem alone.

2 Detailed Labeling Recommendations

a. Clinical Pharmacology section

Pharmacokinetics subsection

Under "Aprepitant after Fosaprepitant Administration" (page 2)

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b. The first paragraph in General under Precaution section (page 8) should be read as below.

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c. Clinical Pharmacology section

Pharmacokinetics subsection

Under Metabolism (page 3)

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d. Precautions Section

Effect of Aprepitant on the Pharmacokinetics of Other Agents Subsection
(page 11)

The following statement should be revised to add the number of subjects and standard deviations to the blood pressure change.

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3 Appendices

3.1 Proposed labeling

EMEND[®]
(fosaprepitant dimeglumine)
For Injection

DESCRIPTION

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19 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

3.2 Individual Study Reviews

Review of the newly submitted blood pressure data of DDI Study

The clinically significant decreases in blood pressures in individual patients when taking fosaprepitant with diltiazem versus taking diltiazem alone are listed below for individual patients.

Individual Listing of Diastolic Blood Pressure (mmHg) and Aprepitant Plasma Concentration (ng/ml) on Day 8 Following Diltiazem With and Without Fosaprepitant

Subject 1601

Alloc	Hour	Diltiazem With Fosaprepitant			Diltiazem Alone			Treatment Difference	Aprepitant Concentration
		Value	Baseline	Change	Value	Baseline	Change		

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Subject 1602

Alloc	Hour	Diltiazem With Fosaprepitant			Diltiazem Alone			Treatment Difference	Aprepitant Concentration
		Value	Baseline	Change	Value	Baseline	Change		

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Subject 1603

Alloc	Hour	Diltiazem With Fosaprepitant			Diltiazem Alone			Treatment Difference	Aprepitant Concentration
		Value	Baseline	Change	Value	Baseline	Change		

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Subject 1604

Alloc	Hour	Diltiazem With Fosoprepitant			Diltiazem Alone			Treatment Difference	Aprepitant Concentration
		Value	Baseline	Change	Value	Baseline	Change		

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Subject 1605

Alloc	Hour	Diltiazem With Fosoprepitant			Diltiazem Alone			Treatment Difference	Aprepitant Concentration
		Value	Baseline	Change	Value	Baseline	Change		

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Alloc	Hour	Diltiazem With Fosaprepitant			Diltiazem Alone			Treatment Difference	Aprepitant Concentration
		Value	Baseline	Change	Value	Baseline	Change		
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Subject 1610

Alloc	Hour	Diltiazem With Fosaprepitant			Diltiazem Alone			Treatment Difference	Aprepitant Concentration
		Value	Baseline	Change	Value	Baseline	Change		
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Subject 1703

Alloc	Hour	Diltiazem With Fosaprepitant			Diltiazem Alone			Treatment Difference	Aprepitant Concentration
		Value	Baseline	Change	Value	Baseline	Change		
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Table 4 Frequency of blood pressure decrease of greater than 20mmHg between any two consecutive measurements of less than 20 minutes apart (Day 8)

Subject #	Diltiazem With Fosaprepitant	Diltiazem
1601		
1602*		
1603		
1604		
1605		
1606		
1608		
1609		
1610		
1703		

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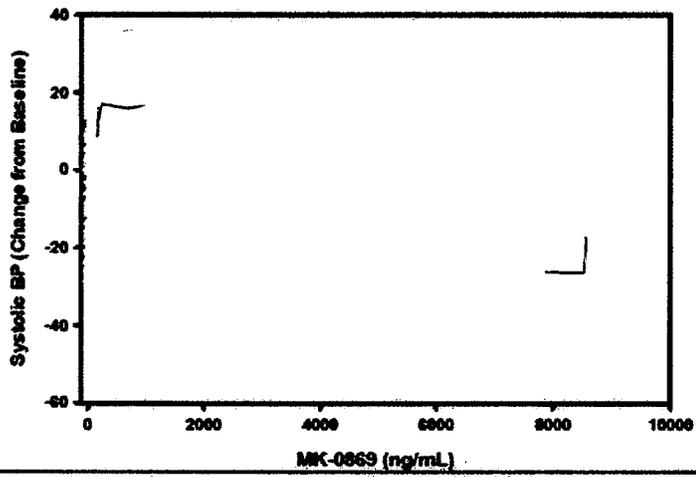
Data from individual listing of systolic blood pressure (mmHg) on Day 8 following diltiazem with and without fosaprepitant

* Data were missing between 2 to 2.5 hr post dose of diltiazem + fosaprepitant while the data from the same period for diltiazem alone were not.

Summary: Eight subjects experienced greater than 20 mmHg blood pressure decrease when diltiazem was coadministered with fosaprepitant while only 5 subjects experienced such blood pressure decrease when diltiazem was administered alone.

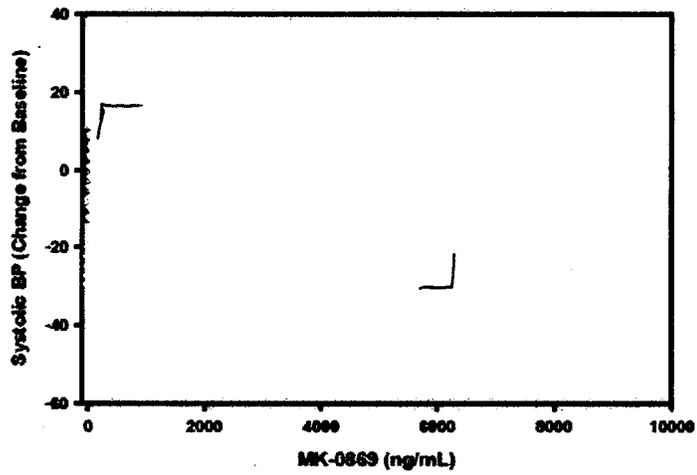
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Systolic Blood Pressure versus Plasma MK-0869 Concentrations
Following MK-0517 Dose Administration Alone on Day 8



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Systolic Blood Pressure versus Plasma MK-0869 Concentrations
Following Diltiazem and MK-0517 Dose Administration on Day 8



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Individual Listing of Maximum Decrease from Baseline in Blood Pressure (mmHg) on Day 8 Following Diltiazem With and Without Fosaprepitant

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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Reviewer's comments:

Concomitant administration of diltiazem and fosaprepitant resulted in higher exposure to diltiazem.

The individual subjects' data showed that co-administration of diltiazem and fosaprepitant caused further decrease in blood pressure beyond that caused by diltiazem alone. The time courses of blood pressure measurement and diltiazem plasma concentrations only shared a few common time points. The sporadic

same time points between the PK and PD measurements do not render a concrete support for making a correlation between the plasma concentration of diltiazem and the extent of blood pressure further decrease.

The data in the table listed above showed that subjects experienced more episodes of greater than 20 mmHg decrease in blood pressure when taking diltiazem and fosaprepitant concurrently than when taking diltiazem alone.

The data in the table listed above showed that subjects experienced more episodes of greater than 13 mmHg decrease in blood pressure when taking diltiazem and fosaprepitant concurrently than when taking diltiazem alone.

A sudden decrease in blood pressure can be dangerous. For example, a decrease of 20mmHg (from 130 systolic to 110 systolic) can cause dizziness and fainting due to the brain failing to receive adequate blood supply. (<http://www.mayoclinic.com/health/low-blood-pressure>).

From the clinical pharmacology perspective, co-administration of fosaprepitant and diltiazem may cause serious adverse events resulting from clinically significant decreases in blood pressure beyond that caused by diltiazem alone.

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3.3 Consult Review of Division of Cardiovascular and Renal Products



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)

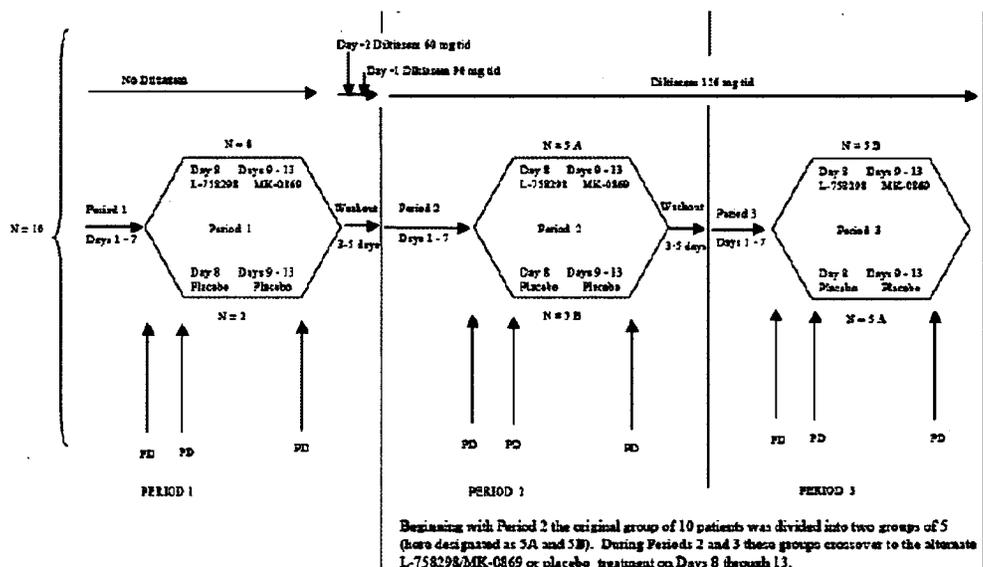
This memo responds to your consult to us dated November 16, 2007, requesting our comments on the blood pressure changes with the combination of fosaprepitant and diltiazem in Study 011. Fosaprepitant is the N-phosphoryl, water-soluble prodrug of aprepitant, an approved oral antiemetic aprepitant (Emend[®]) 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 desacyldiltiazem 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

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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

(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.”

From this later submission we have included an example of the DBP values for one patient in Table 5 and example of the maximum changes from baseline for diltiazem with and without fosaprepitant in Table 6.

Table 5: Example of DBP Values for One Patient

Alloc	Hour	Diltiazem With Fosaprepitant			Diltiazem Alone			Treatment Difference	Aprepitant Concentration
		Value	Baseline	Change	Value	Baseline	Change		
1601									

b(4)

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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CLINICAL PHARMACOLOGY REVIEW

NDA: 22-023	Submission Dates: 3/31/06, 7/28/06, 2/12/07
Brand Name	Emend
Generic Name	Fosaprepitant Dimeglumine
Reviewer	Sue-Chih Lee, Ph.D.
Deputy Division Director	Hae-Young Ahn, Ph.D.
OCP Division	Division of Clinical Pharmacology III
OND Division	Division of Gastroenterology Products
Sponsor	Merck
Submission Type	Original NDA, NME
Formulation; Strength(s)	Injection, 115 mg/10 mL
Dosing regimen	Single 115 mg administered 30 minutes prior to chemotherapy (as a substitute for oral Emend 125 mg) on Day 1 only
Indication	Prevention of chemotherapy-induced nausea and vomiting (CINV)

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1. EXECUTIVE SUMMARY

The proposed drug product contains fosaprepitant dimeglumine (also designated as L-758298 or MK-0517) as its active ingredient and is intended for IV administration. Fosaprepitant is a prodrug of aprepitant (also designated as L-754030 or MK-0869), which is an antagonist of neurokinin 1 (NK₁) receptors. Oral aprepitant has been approved for the prevention of acute and delayed nausea and vomiting due to highly emetogenic and moderately emetogenic cancer chemotherapy (CINV) when used in combination with other antiemetic agents such as a 5-HT₃ receptor antagonist and a corticosteroid. The currently approved 3-day CINV dosing regimen for oral aprepitant is 125 mg on Day 1 followed by 80 mg on Days 2 and 3. The sponsor is pursuing the approval of intravenously administered fosaprepitant dimeglumine as an alternative for the first day of the 3-day oral dosing regimen, i.e., IV infusion of fosaprepitant 115 mg over 15 minutes will be administered 30 minutes before chemotherapy on Day 1 and oral aprepitant 80 mg on Days 2 and 3.

No Phase 3 clinical trials in the target patient population were conducted for the IV fosaprepitant formulation. To support this application, the sponsor provided data from 25 Phase 1 and Phase 2 studies involving various formulations, doses, infusion durations and indications. Out of these studies, three (relative bioavailability, drug interaction with midazolam, drug interaction with diltiazem and thorough QT studies) provide new clinical pharmacology information that is relevant to this application. The review of the thorough QT study by the QT-IRT Team is presented in a separate document. Additionally, two published articles related to dexamethasone dose response were also provided and reviewed.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed this NDA and found that the overall Clinical Pharmacology Section is acceptable provided that a mutually satisfactory agreement can be reached at a later time between the sponsor and Agency regarding the labeling language. The comments below, although not approval issues, should be communicated to and addressed by the sponsor.

1.2 Comments

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.

1.3 Phase IV Commitments

None

1.4 Summary of Clinical Pharmacology Findings

Pharmacokinetic parameters of fosaprepitant and aprepitant following IV administration of fosaprepitant:

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 postdose 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}.

Drug-drug interactions

Midazolam:

IV fosaprepitant 100 mg increased the midazolam AUC by 60% but did not increase midazolam C_{max} when it was coadministered with oral midazolam 2 mg. Dosage adjustment for midazolam may be necessary when midazolam is coadministered with IV fosaprepitant 115 mg depending on the clinical situation (e.g., elderly patients) and degree of monitoring available.

Diltiazem:

Effect of diltiazem on fosaprepitant PK: Following single IV dose of fosaprepitant 100 mg in hypertensive patients receiving oral diltiazem 120 mg TID, aprepitant AUC and Cmax were ~45% and 20% higher, respectively, compared to those from administration of fosaprepitant alone. This effect is thought to be due to inhibition of CYP3A4 by diltiazem. No dosage adjustment is necessary for fosaprepitant when it is coadministered with diltiazem.

Effect of fosaprepitant on diltiazem PK: Coadministration of single IV fosaprepitant 100 mg with oral diltiazem 120 mg increased AUC by ~40% for diltiazem, ~35% for desacetyldiltiazem, and ~11% for N-monodesmethyl-diltiazem compared to diltiazem administered alone. These effects are considered to be the result of CYP3A4 inhibition by aprepitant.

Effect of fosaprepitant on blood pressure in hypertensive patients receiving diltiazem:

A single 100-mg IV dose of fosaprepitant when given with 120-mg oral doses of diltiazem administered 3 times daily resulted in a small but clinically meaningful decrease in diastolic blood pressure (-2.6 mmHg) and systolic blood pressure (-6.0 mmHg) beyond those changes induced by diltiazem alone. For a closer evaluation of the data, an information request will be made.

Dexamethasone:

In the proposed labeling for IV fosaprepitant, the sponsor keeps the same dosing recommendation for dexamethasone as that seen in the approved labeling for oral aprepitant. Because drug interaction is expected to be less with IV fosaprepitant 115 mg compared to oral aprepitant 125 mg, keeping the same dexamethasone dose can result in lower dexamethasone concentrations. As such, the antiemetic efficacy derived from dexamethasone dose may be somewhat lower when IV fosaprepitant is administered in lieu of oral aprepitant.

Implication of the clinical pharmacology information on the safety and efficacy assessment of IV fosaprepitant

Efficacy:

- The relative bioavailability data obtained from Study Protocol 012L1 appear to support the efficacy of the alternative 3-day CINV regimen in which IV fosaprepitant 115 mg infused over 15 minutes is administered on Day 1 in lieu of the oral aprepitant 125 mg.
- Dexamethasone, when given at the same dose as in the oral aprepitant regimen, may result in somewhat lower antiemetic efficacy on Day 1 due to the lower dexamethasone concentrations expected when IV fosaprepitant is used in lieu of oral aprepitant. This point was communicated to Dr. Wen-Yi Gao, Medical Officer of the Division of Gastroenterology Products.

Safety:

- QT: The sponsor conducted a thorough QT study to assess the QT prolongation potential following IV administration of fosaprepitant. According to Dr. Christine Garnett, Pharmacometrician of OCP and a member of the QT-IRT Team, there was no QT signal for the suprathreshold dose of IV fosaprepitant 200mg infused over 15 minutes.

- The pharmacokinetic information indicates that the safety database for oral aprepitant at high doses may be used to support the safety of high aprepitant C_{max} (mean: 3095 ng/mL) observed with IV fosaprepitant. Oral aprepitant 375 mg resulted in a mean C_{max} of 4194 ng/mL after a single dose and >6000 ng/mL at “steady state.” Thus, the safety data obtained from oral aprepitant 375 mg are useful.
- The safety with respect to the systemic exposure of fosaprepitant, although for less than an hour following infusion, has to be evaluated from the clinical data preferably in subjects receiving IV fosaprepitant at the dose of at least 115 mg and with an infusion duration of no more than 15 minutes. The safety of the phosphate (18.3 mg) and meglumine (73 mg) released from fosaprepitant 115 mg may be assessed from nonclinical information and clinical data in subjects receiving IV fosaprepitant.

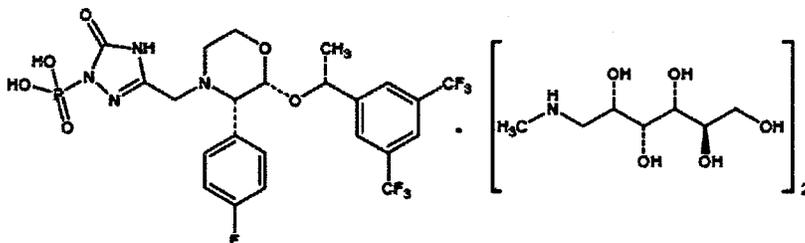
2. QUESTION-BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physicochemical properties of the drug substance and drug product?

Drug Substance:

The chemical structure of fosaprepitant dimeglumine is shown below. The free base has three chiral centers and each meglumine counter ion has four additional chiral centers. It is chemically described as 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one]. The empirical formula is C₂₃H₂₁F₇N₄O₃ with a molecular weight of 1004.83.



Fosaprepitant has 4 pK_a values: 3.05±0.03, 4.92±0.02, 9.67±0.01 and 10.59±0.03. The solubility of fosaprepitant dimeglumine is 90 mg/mL in room temperature saline (or 55 mg/mL free acid equivalent). Fosaprepitant dimeglumine is amorphous and is not sensitive to light or oxygen. However, it is unstable when stored at room temperature or under refrigeration, but it is stable when stored at -20°C.

Drug Product:

Fosaprepitant Dimeglumine for Injection is supplied as a sterile lyophilized formulation for reconstitution and dilution prior to intravenous infusion. Each 10 mL vial contains fosaprepitant dimeglumine (115 mg of fosaprepitant free acid) in a lyophilized Polysorbate 80 is included in the formulation to . The formulation of fosaprepitant dimeglumine IV solution prior to lyophilization is presented in Table 1. The final solution for IV infusion contains 115 mg fosaprepitant and polysorbate 80 in 10 mL of injection.

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Table 1: Components and composition of fosaprepitant dimeglumine IV solution prior to lyophilization

Component	Reference	Function	mg/mL [†]
Fosaprepitant Dimeglumine			
Edetate Disodium	USP/Ph. Eur.		
Polysorbate-80	NF/Ph. Eur.		
Lactose Anhydrous	NF/Ph. Eur.		
Sodium Hydroxide	NF/Ph. Eur.		
Hydrochloric Acid	NF/Ph. Eur.		
	USP/Ph. Eur.		

† Adjusted weight for purity and moisture
 § pH is adjusted to 9.2±0.1, if necessary.

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2.1.2 Why is fosaprepitant, instead of aprepitant, used in the IV formulation?

Aprepitant itself cannot be formulated into an intravenous formulation at a high enough dose to be clinically efficacious due to solubility problems. Fosaprepitant dimeglumine is the bis-meglumine salt of phosphorylated aprepitant. The improved aqueous solubility of fosaprepitant dimeglumine permits development of an IV formulation. It is converted into aprepitant in vivo.

2.1.3 What are the proposed mechanism of action, therapeutic indication and dosage recommendation?

Mechanism of action:

Fosaprepitant is a water-soluble prodrug of aprepitant. However, in vitro studies showed that fosaprepitant was as potent as aprepitant in NK₁ receptor binding. Following IV administration, fosaprepitant is readily converted to aprepitant and, therefore, the pharmacological effect of IV fosaprepitant is primarily derived from aprepitant formed.

Proposed indication and dosage regimen:

Currently, oral aprepitant is approved for use in the prevention of chemotherapy induced nausea and vomiting (CINV) with a dosing regimen of 125 mg on Day 1 prior to chemotherapy and 80 mg on Days 2 and 3. IV fosaprepitant 115 mg is to be used in place of the first dose of oral aprepitant 125 mg for CINV while the same oral aprepitant dose (80 mg) will be given on Days 2 and 3.

2.2 General Clinical Pharmacology

2.2.1 What data has the sponsor provided to support the safety and efficacy of IV fosaprepitant?

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 C_{max} 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 C_{max} 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 0.61 mg/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 is an acceptable pharmaceutical salt used in other marketed products such as lansoprazole and telmisartan but a search of PDR showed that none of these products has an active ingredient that exists as a meglumine salt. 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.

Safety evaluation of IV fosaprepitant is being conducted by Dr. Yi-Wen Gao, Medical Officer of HFD-180.

2.2.2 How is fosaprepitant metabolized following IV administration?

Following intravenous administration, fosaprepitant was rapidly converted into aprepitant. The conversion of fosaprepitant to aprepitant were studied in a variety of preparations including whole blood, human liver preparations, and in fractions from major human organs, including liver, kidney, lung, and ileum. Fosaprepitant was converted to aprepitant at similar rates in all tissues examined. At this time, the exact identity of the enzyme(s) involved in the conversion of

fosaprepitant to aprepitant has not been identified. Since conversion of the fosaprepitant to aprepitant involves hydrolysis of the phosphoramidate moiety and can occur in the absence of NADPH, conversion of fosaprepitant to aprepitant is not thought to involve the CYP family of enzymes.

The metabolic pathway for aprepitant was provided in the original NDA for oral aprepitant.

2.2.2 How is the dose and infusion duration determined for IV fosaprepitant?

The dose and infusion duration of fosaprepitant were determined from relative bioavailability studies comparing IV fosaprepitant to oral aprepitant. The target dose for IV fosaprepitant is the dose that results in aprepitant concentration profiles similar to those for oral aprepitant 125 mg. Various doses (including the 90-mg, 100-mg, 115-mg doses) and infusion duration (30 sec to 30 min) were studied. The 115-mg fosaprepitant dose infused over 15 minutes was selected as it best mimicked the profile of the oral aprepitant 125 mg (figure 1).

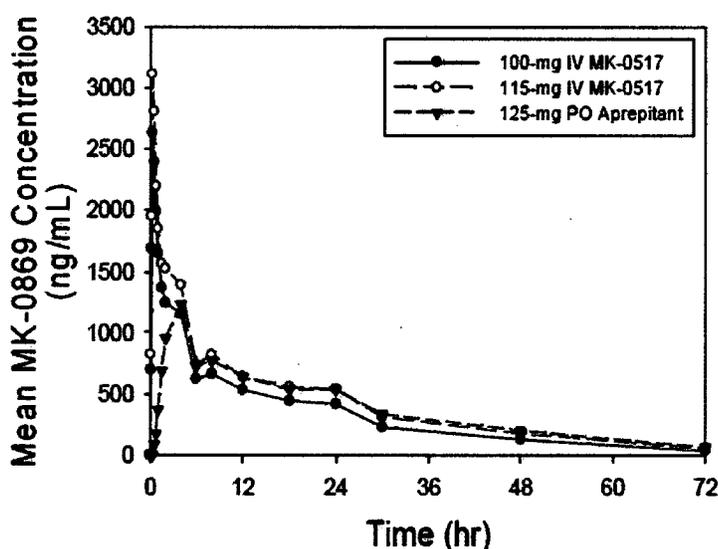


Figure 1: Mean Plasma Aprepitant Concentration Profiles Following 100-mg and 115-mg IV Fosaprepitant administered over 15 minutes and 125-mg PO Aprepitant (Part V; Protocol 012L1)

2.2.3 What are the pharmacokinetic parameters following IV administration of fosaprepitant in healthy subjects?

Following IV administration, fosaprepitant plasma levels fell near or below the lower limit of quantitation (10 ng/mL) within 30 minutes after the end of infusion in all subjects evaluated and conversion of fosaprepitant to aprepitant was nearly complete. The elimination half-life for fosaprepitant was estimated to be 2-3 minutes. Mean fosaprepitant C_{max} was approximately 5900 ng/mL and mean AUC was 1483 ng.h/mL. Note that fosaprepitant concentration at 10 minutes after the start of IV infusion was higher than that at the end of infusion (Figure 2). This is likely to be due to the error in sampling time since the conversion to aprepitant was very rapid.

Mean fosaprepitant AUC was approximately 5% of mean aprepitant AUC. As such, the efficacy of IV fosaprepitant is expected to be primarily derived from aprepitant formed following injection.

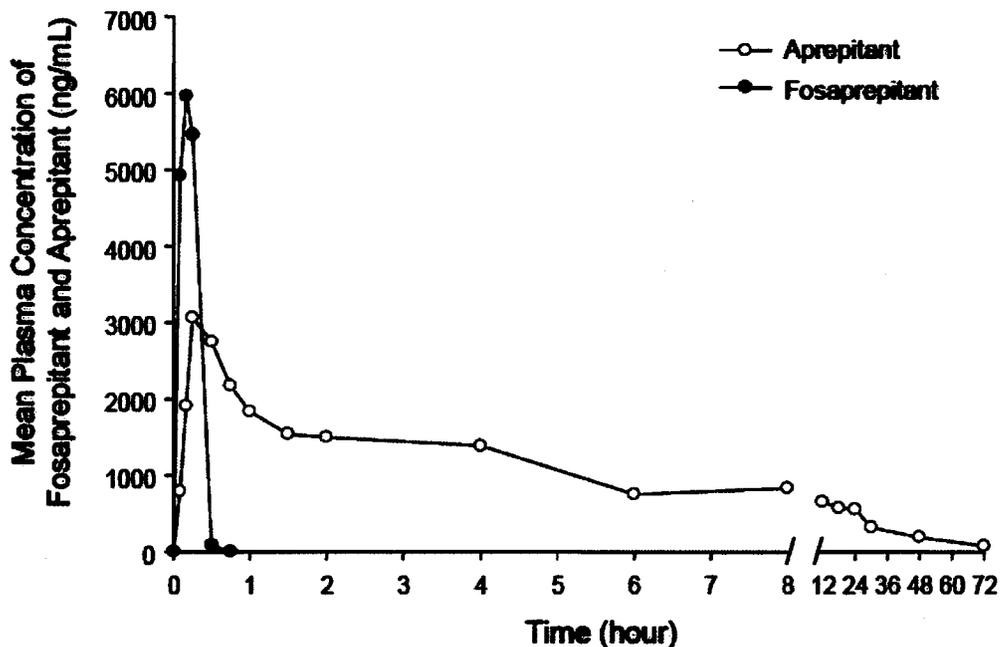


Figure 2: Mean Plasma Concentration of Fosaprepitant and Aprepitant Following 115-mg IV Fosaprepitant Administered as a Constant Rate Infusion Over 15 Minutes

Table 2: Mean PK parameters for fosaprepitant and aprepitant following IV administration of fosaprepitant 115 mg

Parameter	Analyte	
	Fosaprepitant	Aprepitant
Conc*, ng/mL	5635 ± 1544	3267 ± 1159
AUC, ng.h/mL	1483 ± 300	31724 ± 14287

* C_{15min} (at end of infusion) for fosaprepitant; C_{max} for aprepitant

2.2.4 How does the pharmacokinetics following IV administration of fosaprepitant 115 mg compare to that following oral administration of aprepitant 125 mg? What are the implications?

Following IV administration of fosaprepitant 115 mg to healthy subjects, plasma aprepitant concentrations were higher than those observed with oral aprepitant 125 mg for the first 4-5 hours postdose 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 comparative pharmacokinetic data supports the efficacy of IV fosaprepitant but not safety.

Table 3: Geometric Mean Pharmacokinetic Parameters of Aprepitant Following Administration of 125-mg Oral Aprepitant and 115-mg IV Fosaprepitant, their ratio and 90% Confidence Intervals

PK Variable	Geometric Mean [†] 125-mg Aprepitant	Geometric Mean [†] 115-mg IV Fosaprepitant	Geometric Mean Ratio (IV/Oral) (90% CI)	MSE [‡]
AUC _{0-∞} (ng·hr/mL)	26318	29611	1.13 (1.06,1.20)	0.0471
C _{max} (ng/mL)	1254	3095	2.47 (2.25,2.71) [§]	0.0755
C _{24 hr} (ng/mL)	494	504	1.02 (0.94,1.11) [§]	0.0600
T _{max} (hr)	4.0	0.25	-	-
t _{1/2} (hr)	14.0	13.6	-	-

[†] Median for T_{max} and harmonic mean for t_{1/2}.
[‡] Mean Square Error on natural log- scale.
[§] 95% CI.

2.3 Intrinsic Factors

The sponsor has evaluated intrinsic factors in the original NDA and the information is reflected in the current Emend[®] label. There is no new information on intrinsic factor in this NDA.

2.4 Extrinsic Factors

Drug-Drug Interaction

Due to instability in microsomal or hepatic cultures, fosaprepitant could not be adequately evaluated *in vitro* for its potential for CYP inhibition or induction. However, the sponsor provided data from two *in vivo* drug interaction studies. One studied interaction with midazolam and the other with diltiazem. In addition, the sponsor provided two articles to support the dexamethasone dose proposed as part of the anti-emetic regimen.

Interaction with Midazolam

The sponsor conducted a study in 8 healthy subjects to evaluate the effect of IV fosaprepitant 100 mg on the pharmacokinetics of oral midazolam 2 mg. This was an open-label, 2-period, crossover study. The results indicated that IV fosaprepitant 100 mg increased the midazolam AUC to 1.6-fold (Figure 3; Table 4). No increase in the C_{max} of midazolam was observed when oral midazolam was coadministered with IV fosaprepitant. It is noted that a previous study showed that oral aprepitant 125 mg administered as a single dose increased the oral midazolam AUC to 2.3-fold. Based on these observations, the substitution of fosaprepitant for aprepitant on Day 1 of the CINV regimen is expected to produce a drug-drug pharmacokinetic interaction profile that is no greater than that with oral aprepitant.

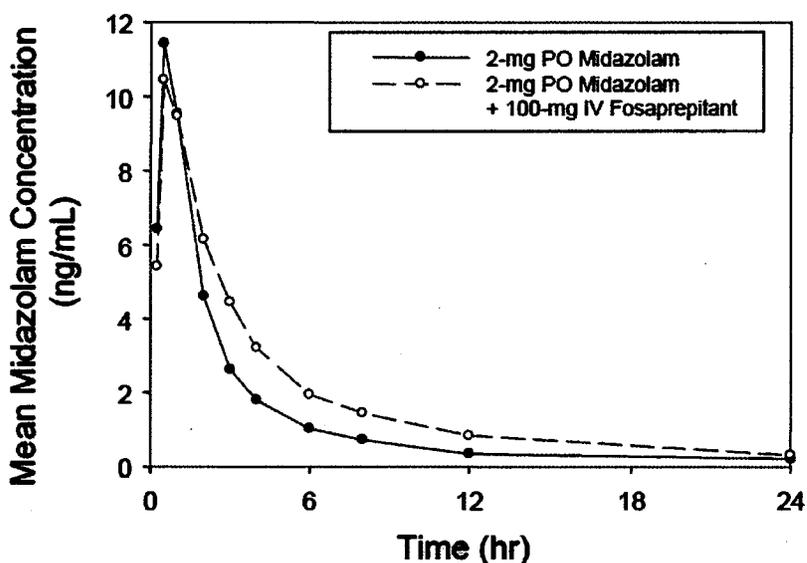


Figure 3: Mean Plasma Concentration Profiles of Midazolam Following 2-mg PO Midazolam Alone and 2-mg PO Midazolam with 100-mg IV Fosaprepitant

Table 4: Mean Midazolam AUC Following oral administration of midazolam 2 mg with and without concomitant IV fosaprepitant 100 mg

Study Part	Comparison (Test vs. Reference)	Geometric Mean		GM Ratio (Test/Reference)	90% Confidence Interval
		MDZ with MK-0517	MDZ alone		
Part II (N=8)	Midazolam 2-mg with 100 mg IV MK-0517 PS80 vs. Midazolam 2-mg alone	44.6	28.0	1.60	(1.41, 1.81)

Interaction with diltiazem

A drug interaction study with diltiazem was conducted in 10 hypertensive patients. This was a double-blind, randomized, placebo-controlled, 3-period fixed sequence study to evaluate the pharmacokinetic and pharmacodynamic interaction for fosaprepitant/diltiazem and aprepitant/diltiazem, respectively. (This study was submitted in the NDA for oral aprepitant but the information related to interaction with IV fosaprepitant was not included in the original review.)

The study design is depicted in a schematic diagram as shown below. Prior to the start of the study, patients had a 1- to 2-week washout from prior hypertensive medication.

In Period 1, patients received no medications for 7 days. On Day 8, patients were given 100 mg of fosaprepitant (L-758298) or placebo as a 15-minute IV infusion followed by 5 days (Days 9 to 13) of single oral 300-mg doses of aprepitant (a different formulation; bioavailability equivalent to 230 mg of the currently marketed formulation) or placebo 30 minutes after a standard breakfast.

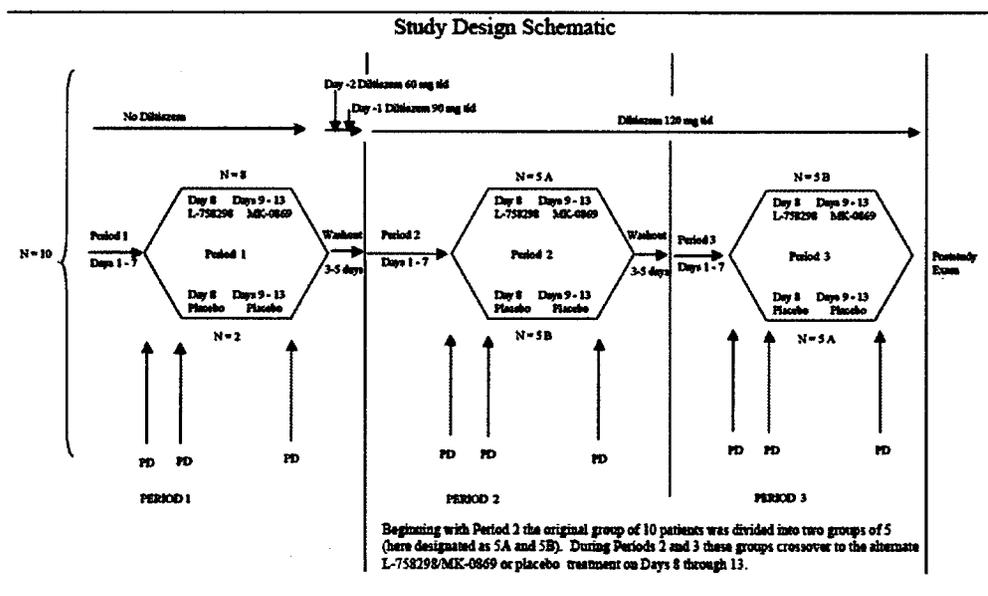
b(4)

In each treatment period, a 2-mg IV dose of midazolam was administered over 2 minutes either alone (Treatment 1) or 1 hour after a 125-mg dose of aprepitant (Treatment II). The sequence of the treatments was randomly assigned and there was at least 14 days between treatment periods (Period 1 and Period 2).

In Period 2, all patients were titrated up to a 120-mg oral dose of diltiazem 3 times daily, which was continued through the end of Period 3 and until the poststudy visit.

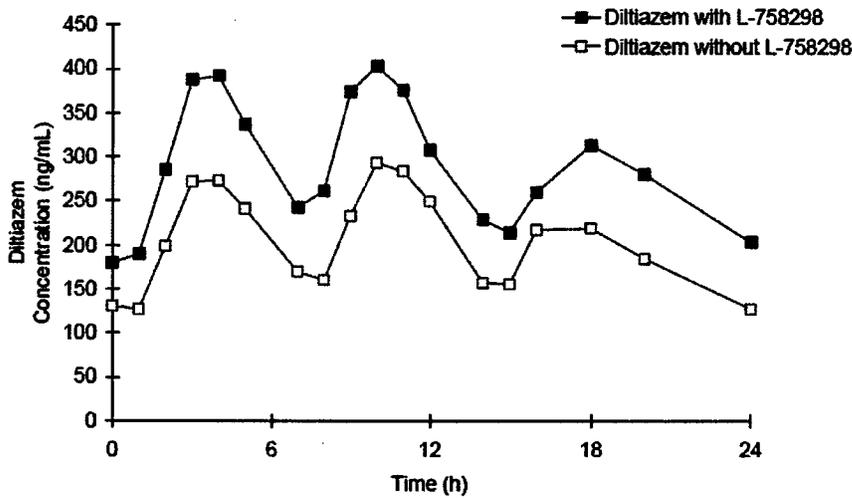
During Period 2, in addition to diltiazem treatment, patients were randomized to receive either placebo or fosaprepitant (IV fosaprepitant 100 mg on Day 8, and oral aprepitant 300 mg on Days 9 to 13). In Period 3, patients crossed over to the alternate fosaprepitant or placebo treatment in addition to the diltiazem treatment.

b(4)



Effect of fosaprepitant on diltiazem PK:

Coadministration of single IV fosaprepitant 100 mg with oral diltiazem increased plasma diltiazem concentrations as shown in Figure 4. The increase in AUC_{0-24hr} was ~40% for diltiazem, ~35% for desacetyldiltiazem, and ~11% for N-monodesmethyl-diltiazem compared to diltiazem administered alone (Table 5). Note that diltiazem C_{max} increased by 46%. These increases in the exposure for diltiazem and its metabolites are the result of CYP3A4 inhibition by fosaprepitant.



L-758298 = Fosaprepitant

Figure 4: Mean (N=9) Plasma Concentration Profiles of Diltiazem During Administration of Diltiazem With Fosaprepitant or Placebo (Protocol 011)

b(4)

Table 5: Pharmacokinetic Parameters for Diltiazem Following Dosing of Diltiazem With and Without A Single Intravenous Dose of Fosaprepitant or Daily Oral Doses of Aprepitant

b(4)

	Geometric Mean		Geometric Mean Ratio (With/Without)	90% Confidence Interval	p-Value
	Diltiazem With Fosaprepitant [†]	Diltiazem Without Fosaprepitant [†]			
AUC _{0-24 hr} (ng·hr/mL)	6636.36	4752.19	1.40	(1.23, 1.58)	0.001
C _{max} (ng/mL)	422.81	289.36	1.46	(1.24, 1.72)	0.003
	Diltiazem With Aprepitant	Diltiazem Without Aprepitant			
AUC _{0-24 hr} (ng·hr/mL)	8496.53	5114.59	1.66	(1.44, 1.92)	<0.001
C _{max} (ng/mL)	472.49	306.58	1.54	(1.34, 1.77)	0.001

[†] After the first dose of diltiazem.

Effect of IV fosaprepitant on PD parameters in hypertensive patients receiving diltiazem:

A single 100-mg intravenous dose of fosaprepitant when given with 120-mg oral doses of diltiazem administered 3 times daily did not result in a clinically meaningful PR prolongation or change in heart rate beyond those changes induced by diltiazem alone, but did result in a small but clinically meaningful decrease in systolic blood pressure (-6.0 mmHg), and may result in a small but clinically meaningful decrease in diastolic blood pressure (-2.6 mmHg) beyond those changes induced by diltiazem alone (Table 6).

Table 6: Effect of Coadministration of IV Fosaprepitant on the Pharmacodynamic Parameters in Hypertensive Patients Receiving Oral Diltiazem

	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

Effect of diltiazem on fosaprepitant PK:

Aprepitant exposures (AUC) after IV administration of fosaprepitant with diltiazem were increased ~45% over those from administration of fosaprepitant alone. This increase is consistent with moderate inhibition of CYP3A4 by diltiazem. The increase in aprepitant C_{max} was estimated to be 20% following coadministration of fosaprepitant IV 100 mg with oral diltiazem.

Table 7: Pharmacokinetic Parameters for Aprepitant Following Intravenous Single Dose of 100-mg Fosaprepitant — Alone or With Diltiazem

b(4)

Pharmacokinetic Parameter	Geometric Mean		Geometric Mean Ratio (Fosaprepitant With/Without Diltiazem)	90% CI	p-Value
	Fosaprepitant With Diltiazem (N=6)	Fosaprepitant Without Diltiazem (N=6)			
AUC _{0-24 hr} (ng•hr/mL)	18843.00	13004.08	1.45	(1.17, 1.79)	0.017
C _{max} (ng/mL)	1729.15	1439.07	1.20	(0.99, 1.46)	0.120

Drug interaction with dexamethasone:

The sponsor did not conduct a study to investigate the effect of IV fosaprepitant on the dexamethasone PK. Dexamethasone is routinely included in the antiemetic regimen for CINV. Due to inhibition of the CYP3A4 activity by oral aprepitant, oral dexamethasone dose is reduced in half when it is given with oral aprepitant. IV fosaprepitant is expected to interact with orally administered CYP3A4 substrates to a lower degree relative to oral aprepitant. This means that the oral dexamethasone levels attained with IV fosaprepitant may be lower than when oral aprepitant is administered on Day 1 of the 3-day regimen.

The sponsor claimed that published literature* indicated that the dexamethasone antiemetic dose response was relatively flat: in one HEC study there was no significant difference in prevention of CINV between IV dexamethasone 12 mg and 20 mg and in a MEC study there was no significant difference between IV dexamethasone 8 mg and 24 mg. Hence, the lower dexamethasone exposure resulting from the substitution of IV fosaprepitant for oral aprepitant is not expected to result in diminished antiemetic efficacy in preventing CINV. As such, no change in the recommended dexamethasone dose in the regimen is proposed when intravenous fosaprepitant substitutes for oral aprepitant.

It is noted that in the study where patients received cisplatin chemotherapy, dexamethasone 20 mg given intravenously was most efficacious compared to 4 mg, 8 mg and 12 mg. Although there was no statistically significant difference in acute vomiting between dexamethasone 20 mg and 12 mg, the 20 mg dose (but not the 12 mg) was statistically better than 8 mg or 4 mg. Still, the difference in results between the 12 mg and 20 mg doses was small (Table 8). A discussion was made with Dr. Yi-Wen Gao, Medical Officer of HFD-180, and he was not concerned about this small difference and the implication on the NDA.

Table 8: Results on Acute Vomiting and Nausea in Patients Receiving Dexamethasone at 4, 8, 12 or 20 mg

	Dexamethasone				P
	4 mg	8 mg	12 mg	20 mg	
No. of patients	133	136	130	131	
Rate of complete protection from vomiting	69.2	69.1	78.5	83.2	< .02
Rate of complete protection from nausea	60.9	61.0	66.9	71.0	NS
Intensity of acute vomiting, † no. of emetic episodes, mean ± SD	4.3 ± 7.0	5.3 ± 8.7	3.2 ± 2.2	3.2 ± 2.6	< .05
Time to the first emetic episode, hours, mean ± SD	10.5 ± 7.5	12.3 ± 7.0	12.1 ± 7.7	13.2 ± 8.6	NS
Intensity of acute nausea, ‡ mean maximal score of nausea	1.54	1.40	1.42	1.39	NS

*References:

1. Italian Group for Antiemetic Research. "Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis" *J Clin Oncol* 1998;16(9):2937-42.
2. The Italian Group for Antiemetic Research. "Randomized, double-blind, dose-finding study of dexamethasone in preventing acute emesis induced by anthracyclines, carboplatin, or cyclophosphamide". *J Clin Oncol* 2004;22(4):725-9.

2.4.1 What is the new drug-drug interaction information to be added to the package insert?

Information on drug interaction with midazolam and diltiazem will be added to the package insert. For midazolam, dosage adjustment may be necessary depending on the clinical situation (e.g., use in elderly patients) and the intensity of patient monitoring. For diltiazem, it appears that a caution statement may suffice for patients taking concomitant IV fosaprepitant due to a small but clinically significant further decrease in systolic and diastolic pressure. However, this matter will be evaluated closer with the Medical Officer. An information request will be made to obtain individual data and summary statistics. (Currently, the effect of concomitant fosaprepitant on the systolic and diastolic pressures was expressed in terms of geometric mean values.)

2.5 General Biopharmaceutics

2.5.1 What dosing recommendations should be made regarding administration in relation to meals?

N/A

2.5.2 Is the proposed to-be-marketed formulation same as the formulation used in the PK studies?

Yes for the relative bioavailability study. However, for the parenteral formulations studied, the formulation itself is not as important as the infusion duration.

2.6 Analytical Methods

2.6.1 Were the assay methods appropriately validated?

Assay of Fosaprepitant and Aprepitant:

Assay of plasma fosaprepitant and aprepitant concentrations was conducted at Merck Laboratory of Westpoint, PA. The assay validation results are acceptable.

Assay of Fosaprepitant: The method was based on solid phase extraction and _____ internal standard (IS). Fosaprepitant and aprepitant were chromatographically separated prior to the thermal conversion of fosaprepitant to aprepitant and a corresponding IS in the heated nebulizer probe (500°C) of the MS/MS system. b(4)

Assay of aprepitant: The assay was based on liquid-liquid extraction of drug from basified plasma. Drug and internal standard _____ or a similar compound) were chromatographed using HPLC and detected by MS/MS. The assay validation results are presented in Table 8. b(4)

Table 8: Assay Validation Results for Fosaprepitant and Aprepitant

Parameter	Fosaprepitant	Aprepitant
Linearity, ng/mL	_____	_____
LLOQ, ng/mL	10	10
Accuracy (% Deviation) Intra-Day Inter-Day	_____	_____
Precision (%CV) Intra-Day Inter-Day	_____	_____
Specificity	No interference observed	No interference observed

b(4)

Assay of Midazolam

Plasma samples collected for assay of midazolam were analyzed by _____

b(4)

_____ The validation results are presented in Table 9.

Table 9: Assay Validation Results for Midazolam

Parameter	Midazolam
Linearity (range)	_____
LLOQ	0.1 ng/mL
Accuracy (% Deviation)	_____
Precision (%CV)	_____ %
Specificity	No interference observed
Stability	Stable at -20°C for 364 days

b(4)

Assay of diltiazem:

Assay for diltiazem and its metabolites in plasma samples was conducted at _____

_____ . This method involves the extraction of _____

b(4)

_____ The data were provided in the oral aprepitant NDA.

3. Detailed Labeling Recommendations

Labeling recommendation will be made at a later time.

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17 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

5. Appendix

Appendix 1: Individual Studies (study design and results)

Protocol #012L1:

A randomized, 5-Part, Intravenous Study of the Safety, Tolerability, Bioequivalence, and Drug Interaction Potential of Final Market Image Formulations of MK-0517 in Young Healthy Subjects

Objectives:

The primary purpose of this study was to identify a dose and formulation of MK-0517 that is safe and well tolerated, and provides an aprepitant plasma exposure (AUC) equivalent to that of a single oral 125-mg dose of aprepitant. Another purpose for this study was to identify a dose of the non-PS80 formulation of MK-0517 that is safe and well tolerated, and provides an aprepitant plasma exposure (AUC) equivalent to that of a single oral 40-mg dose of aprepitant. The other purpose of this study was to assess the inhibitory effects of MK-0517 on CYP3A4 using an oral midazolam probe.

- (1) **Part I—To investigate the safety and tolerability** of intravenous doses of MK-0517 as *two formulations* in young, healthy subjects.
- (2) **Part I—To assess the AUC_{0-∞} equivalence** of one of two (100 mg or 150 mg) single doses of MK-0517 (non-PS80 formulation) and that of an oral 125-mg capsule of aprepitant.
- (3) **Part I—To assess the AUC_{0-∞} equivalence** of one of two (100 mg or 150 mg) single doses of MK-0517 (PS80 formulation) and that of an oral 125-mg capsule of aprepitant.
- (4) **Part I—To assess the AUC_{0-∞} equivalence** of a single dose of 40 mg MK-0517 (non-PS80 formulation) and that of an oral 40-mg capsule of aprepitant.
- (5) **Part II—To investigate the inhibitory effects** of MK-0517 (either PS80 or non-PS80) on CYP3A4 using an oral midazolam probe.
- (6) **Part III—To assess the AUC_{0-∞} equivalence** of a single 90-mg dose of MK-0517 and that of an oral 125-mg capsule of aprepitant, if not met in Part I.
- (7) **Part III – To assess the AUC_{0-∞} equivalence** of a single 40-mg dose of MK-0517 and that of an oral 40-mg capsule of aprepitant, if not met in Part I.
- (8) **Part IV – To further investigate the safety and tolerability** of an intravenous dose of MK-0517 non-PS80 formulation in young, healthy subjects.
- (9) **Part V - To assess the AUC_{0-∞} equivalence** of single doses of 100 and 115 mg MK-0517 PS80 formulation and that of an oral 125-mg capsule of aprepitant.

STUDY DESIGN:

This was a 5-part study in healthy young subjects as summarized in the table below.

Part / Panel	Dose of MK-0517	Form.	Administration	Objective
I / A	100-mg 150-mg	Non-PS80 [§]	Over 5 min	Safety and tolerability; PK comparison to 125-mg oral aprepitant dose.
I / B	100-mg 150-mg	PS80 [†]	Over 15 min	Safety and tolerability; PK comparison to 125-mg oral aprepitant dose
I / C	40-mg	Non-PS80 [§]	Over 2 min	Safety and tolerability; PK comparison to 40-mg oral aprepitant dose
II	100-mg	PS80 [†]	Over 15 min	Effect of MK-0517 administered IV in the PS80 formulation on oral midazolam PK.
III / 1	90-mg	PS80 [†]	Over 15 min	PK comparison to 125-mg oral aprepitant dose
III / 2	40-mg	Non-PS80 [§]	Over 30 sec	Safety and tolerability of MK-0517 administered as Non-PS80
IV	40-mg	Non-PS80 [§]	Over 30 sec	Safety and tolerability of MK-0517 administered as Non-PS80
V	100-mg 115-mg	PS80 [†]	Over 15 min	Definitive bioequivalence of MK-0517 IV PS80 dose to 125-mg oral aprepitant dose.
[†] MK-0517 infusate concentration 1 mg/mL. [§] MK-0517 infusate concentration 12.5 mg/mL				

Part I was a double blind, randomized, 3-panel study.

For Panel A, 12 subjects received MK-0517 (non-PS80 formulation) 100 mg in Period 1 and 150 mg in Period 2 while 2 subjects received the matching placebo in both periods. In the third period all subjects received an oral dose of 125-mg aprepitant market formulation capsule.

Panel B had a similar design to Panel A except that subjects received the PS80 formulation instead of the non-PS80 formulation.

For Panel C, subjects received 40 mg MK-0517 (non-PS80 formulation), or matching placebo in Period 1. In the second period, all subjects received an oral dose of 40-mg aprepitant market formulation capsule.

Part II was an open-label, 2-period drug interaction study. Subjects received 2 mg oral midazolam in the first period and 2 mg oral midazolam with 100 mg of intravenously administered MK-0517 as a PS80 formulation in the second period. All subjects received active treatment in Period 2.

Part III was an open-label, randomized, 2-panel study.

In Panel 1, subjects were assigned to 1 of 2 treatment sequences according to a randomized allocation schedule. All subjects received Treatments A and B on Day 1 of each treatment period in a crossover fashion. Treatment A consisted of a single 125-mg dose of oral aprepitant. Treatment B consisted of a single intravenous dose of 90 mg MK-0517 (PS80 formulation).

In Panel 2 subjects received a single intravenous dose of 40 mg MK-0517 (non-PS80 formulation). This was to be a 2-period crossover with 40-mg oral aprepitant and another dose of MK-0517 should equivalence (in terms of AUC) not have been demonstrated in Part I, Panel C. Since equivalence was met in Part I, Panel C, this panel was conducted as a safety and

tolerability panel with 40-mg MK-0517 (non-PS80 formulation). These changes were made according to protocol.

Part IV was a double blind, randomized, 1-panel study to evaluate MK-0517 non-PS80 formulation at an infusion duration to be between 0.5 and 2 minutes. Subjects received a single intravenous dose of 40 mg MK-0517 (non-PS80 formulation). No plasma samples were collected in Part IV.

Part V was an open-label, randomized, single panel study. This was a 3-period crossover with each subject receiving each of the treatments (E, F, and G). Up to sixty-six (66) healthy male and female subjects were assigned to 1 of 6 treatment sequences according to a randomized allocation schedule. All subjects received Treatments E, F, and G on Day 1 of each treatment period in a crossover fashion. Treatment E consisted of a single 125-mg dose of oral aprepitant. Treatment F consisted of a single intravenous dose of 100 mg MK-0517 (PS80 formulation). Treatment G consisted of a single intravenous dose of 115 mg MK-0517 (PS80 formulation).

Study Subjects:

The number of subjects participated in each part of the study is presented in the table X.

Table: Subject disposition

Part Panel	Part I Panel A	Part I Panel B	Part I Panel C	Part II -
RANDOMIZED:	14	16	14	8 (25-45)
Male (age range)	7 (21-43)	7 (25-34)	4 (25-41)	3 (34-42)
Female (age range)	7 (26-45)	9 (23-44)	10 (22-45)	5
COMPLETED:	14 [†]	14	14	8
DISCONTINUED:	0	2	0	0
Clinical adverse experience	0	0	0	0
Laboratory adverse experience	0	0	0	0
Withdrew Consent	0	2	0	0
Part Panel	Part III Panel 1	Part III Panel 2	Part IV -	Part V -
RANDOMIZED:	34	12	14	76
Male (age range)	13 (19-43)	2 (19-40)	3 (25-34)	36 (20-44)
Female (age range)	21 (19-43)	10 (18-45)	9 (20-45)	40 (19-45)
COMPLETED:	28	11	14	64
DISCONTINUED:	6	1	0	12
Clinical adverse experience	0	0	0	0
Laboratory adverse experience	0	0	0	0
Withdrew Consent	6	1	0	12

[†] AN0008 - 0014 only received 100 mg nonPS80 IV and 125 mg oral. The 150 mg non-PS80 dose was not given to the second half of subjects based on the safety from the first half

Blood Sampling:

Midazolam blood samples were collected in all Periods at the following time points: predose, 15 min, 30 min, 1, 2, 3, 4, 6, 8, 12, and 24 hr.

Analytical Method:

Plasma samples collected for MK-0517 and aprepitant assay were analyzed by the Department of Drug Metabolism, West Point, Merck Research Laboratories (MRL). The analytical method used liquid-liquid extraction for analyte isolation followed by LC/MS/MS detection. The lower limit of reliable quantification (LOQ) was 10 ng/mL.

RESULTS AND CONCLUSION

PS80 formulation for IV infusion (over 15 min):

MK-0517 in the PS80 formulation at a MK-0517 concentration of 1 mg/mL administered over 15 minutes was generally safe and well tolerated at doses up to 150 mg (Part I/B).

Results from other parts of this study concerning the pharmacokinetics of the PS80 formulation of MK-0517 were completed before part V and were used to select dosage levels for evaluation in Part V.

In Part V of this study, both the 100-mg and 115-mg doses of the PS80 formulation of MK-0517 administered intravenously were found to be bioequivalent to an oral aprepitant dose of 125-mg in terms of aprepitant AUC, based on data adjusted for actual IV dose received. The 100-mg dose falls outside the bioequivalence bounds of (0.80, 1.25) based on the un-adjusted analysis. However, either 100-mg or 115-mg dose of the PS80 formulation of MK-0517 had a mean C_{max} greater than 2-fold that of the oral aprepitant 125-mg. The plasma aprepitant concentration at 24 hr postdose following MK-0517 115 mg IV was similar to that following oral aprepitant 125 mg.

MK-0517 115-mg (PS80 formulation administered over 15 min) vs. oral aprepitant 125-mg:

AUC: 1.13 (1.06 – 1.20) (geometric mean ratio & 90% CI)

C_{max}: 2.47 (2.25 – 2.71) (geometric mean ratio & 95% CI; 90% CI not provided)

C_{24hr}: 1.02 (0.94 - 1.11) (geometric mean ratio & 95% CI; 90% CI not provided)

Figure: Mean Plasma Concentration Profiles of Aprepitant Following 100-mg and 115-mg IV MK-0517 (PS80) administered as a 1 mg/mL solution over 15 minutes and 125-mg PO Aprepitant (Part V)

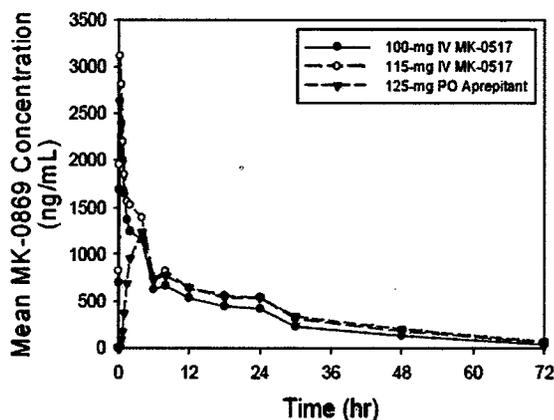


Table: Pharmacokinetic Parameters of Aprepitant Following Administration of 125-mg Oral Aprepitant, and 100-mg and 115-mg IV MK-0517 PS80 Adjusted for Actual IV Dose Received (Part V)

PK Variable	Geometric Mean ¹			Geometric Mean Ratio (IV/Oral) (90% CI)		MSE‡
	125-mg Aprepitant	100-mg IV MK-0517	115-mg IV MK-0517	100-mg IV MK-0517	115-mg IV MK-0517	
AUC _{0-∞} (ng·hr/mL)	26318	22889	29611	0.87 (0.82,0.93)	1.13 (1.06,1.20)	0.0471
AUC _{0-∞} § (ng·hr/mL)	26302	22333	29013	0.849 (0.797,0.904) (0.788,0.915)§	1.103 (1.036,1.174) (1.024,1.188)§	0.0479
C _{max} (ng/mL)	1254	2607	3095	2.08 (1.98,2.28)§	2.47 (2.25,2.71)§	0.0755
C _{21h} (ng/mL)	494	374	504	0.76 (0.69,0.82)§	1.02 (0.94,1.11)§	0.0600
T _{max} (hr)	4.0	0.25	0.25	-	-	-
t _{1/2} (hr)	14.0	13.0	13.6	-	-	-

¹ Least squares estimate. Median for T_{max} and harmonic mean for t_{1/2}.
² Mean Square Error on natural log_e-scale.
³ Results Based on Data Not Adjusted for Actual IV Dose Received.
⁴ 95% CI.

Drug interaction with midazolam:

In Part II of this study, a 100-mg dose of MK-0517 in the PS80 formulation was found to increase the plasma AUC of oral midazolam 1.6-fold.

Study Part	Comparison (Test vs. Reference)	Geometric Mean		GM Ratio (Test/Reference)	90% Confidence Interval
		MDZ with MK-0517	MDZ alone		
Part II (N=8)	Midazolam 2-mg with 100 mg IV MK-0517 PS80 vs. Midazolam 2-mg alone	44.6	28.0	1.60	(1.41, 1.81)

Non-PS80 formulation:

This formulation above 100 mg (infused over 5 min) was not well tolerated. The primary pharmacokinetic result for the non-PS80 formulation was that a 40-mg dose of MK-0517 administered intravenously over 2 min was bioequivalent to a 40-mg dose of aprepitant administered orally *in terms of aprepitant AUC*.

Study Part	Comparison (Test vs. Reference)	Geometric Mean		GM Ratio (Test/Reference)	90% Confidence Interval
		IV	Oral		
BIOEQUIVALENCE TO 40-mg ORAL APREPITANT					
Part I, Panel C	40mg IV non-PS80 vs 40mg PO	7150	6562	1.09	(0.99, 1.19)

Protocol 011: A Double-Blind, Randomized, 3-Period Study to Investigate the Effects of IV L-758298/Oral L-754030 on Diltiazem Pharmacokinetics and Pharmacodynamics in Hypertensive Patients

Investigator: Robert Noveck, M.D., Ph.D., Clinical Research Center, New Orleans, LA.

Study period: 23-Apr-1997 through 06-Aug- 1997

In pharmacologic screening studies, evidence had developed to suggest that MK-0869 might demonstrate calcium channel blockade as an ancillary pharmacologic property. Preclinical studies suggested a potential for interaction with L-type calcium channels in skeletal muscle and studies in dogs suggested an enhanced effects of high doses of diltiazem by MK-0869. In addition, MK-0869 and diltiazem were both known to be metabolized by and have inhibitory effects of CYP3A4. Therefore, it was important to investigate clinically the interaction of MK-0869 with a calcium channel blocker with respect to both safety and pharmacokinetics.

Objectives:

- (1) To investigate the safety and tolerability of concurrent administration of diltiazem and of L-758298 intravenous (IV)/L-754030 (MK-0869) orally.
- (2) To determine the effect of concurrent administration of L-758298 IV/MK-0869 orally and diltiazem orally on PR interval, blood pressure (BP), and heart rate (HR).
- (3) To determine the effect of concurrent administration of L-758298 IV/MK-0869 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 L-758298 IV/MK-0869 orally on electrocardiogram (ECG) indices and HR/BP.
- (5) To investigate the effect of concurrent administration of diltiazem and L-758298 IV/MK-0869 orally on the plasma concentrations of MK-0869, 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.

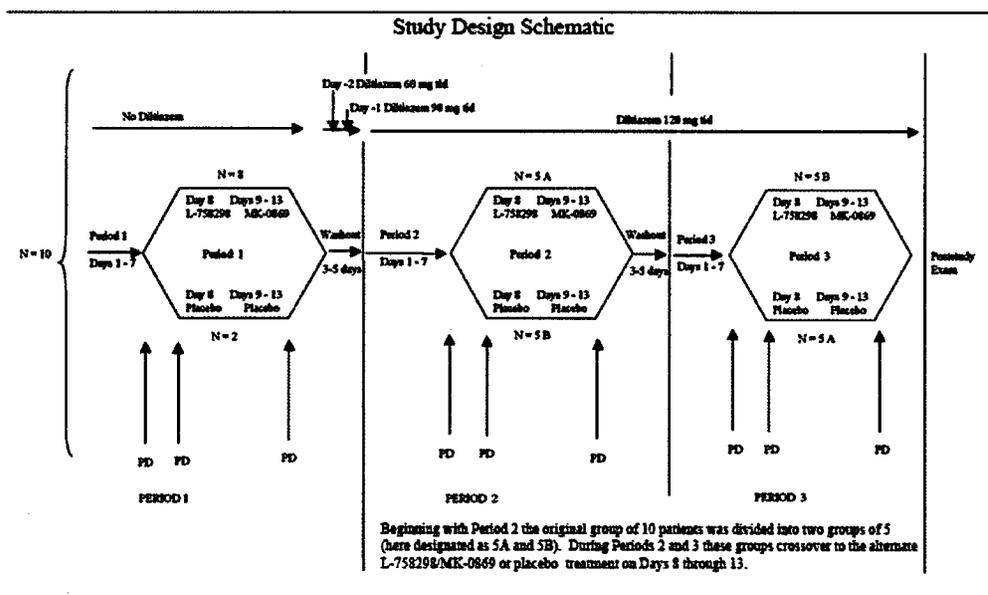
Prior to the start of Period 1, patients had a 1- to 2-week washout from prior hypertensive medication.

In Period 1, patients received no medications for 7 days. On Day 8 they were given 100 mg of L-758298 (fosaprepitant) or placebo as a 15- minute intravenous infusion followed by 5 days (Days 9 to 13) of single oral 300-mg doses of MK-0869 (Phase IIa aprepitant tablet formulation, 30 minutes after a standard breakfast) or placebo alone. Frequent ECG and vital signs monitoring was performed on Days 7 (no medication), 8 (after L-758298), and 13 (after 5 days of MK-0869). There was a 1-week interval between Periods 1 and 2.

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 one period, patients on Day 8 were given a 15-minute intravenous administration of 100 mg of L-758298, and on Days 9 to 13 were administered a single 300-mg oral dose of MK-0869; and in the other period, patients were given placebo to match the L-758298 intravenous administration and placebo to match MK-0869. Frequent ECG and vital signs monitoring was performed on Days 8 (diltiazem 120 mg 3 times daily plus L-758298 or placebo) and 13 (diltiazem 120 mg 3 times daily plus MK-0869 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).



Sampling Scheme and analysis:

Pharmacokinetics: Blood was collected over 24 hours on Day 8 and Day 13, Periods 2 and 3, for plasma MK-0869 analysis and also for diltiazem and diltiazem metabolite assay. Area under the concentration-time curve (AUC), maximum concentration (C_{max}), and time-to-maximum concentration (T_{max}) for MK-0869 were determined after intravenous dosing with L-758298 and after oral dosing with MK-0869/ with and without diltiazem. AUC was also calculated for diltiazem and its 2 metabolites, desacetyldiltiazem and N-monodesmethyl diltiazem, on Days 8 and 13 in Period 2 and 3.

Pharmacodynamics: 12-lead ECGs (PR and QTc intervals) and vital signs (HR and BP) were performed at specific time points throughout the study including frequent measurements on Days 7, 8, and 13 in each period (with exception of Day 7, Period 3).

Analyses: The maximum PR changes from baseline ratios were log-transformed prior to analysis. Change from baseline ratios (postdose measurement/baseline defined as predose Day 8) were calculated for PR and QTc intervals at each time point for each patient on Days 8 and 13 in

each period. On Days 8 and 13, the log-transformed data were analyzed using an analysis of variance (ANOVA) model for a 2-period, crossover design.

Ninety percent confidence intervals for the least square mean difference between treatments on the log scale were calculated. These 90% confidence limits were exponentiated to obtain 90% confidence intervals for the geometric mean ratio ([diltiazem with fosaprepitant IV or oral aprepitant]/[diltiazem with placebo]). If the upper limit of the 90% CI for the maximum geometric mean PR interval ratio was <1.25, then it was concluded that fosaprepitant IV or oral aprepitant given concurrently with diltiazem does not result in a clinically significant PR prolongation beyond those changes induced by diltiazem alone.

The maximum moving average change from baseline for blood pressure and heart rate was analyzed in the same fashion as the log-transformed values of the maximum change from baseline ratios for the PR interval. (The baseline measurement, for Days 8 and 13, was defined as the average of the predose measurements [taken at 20 minutes, 10 minutes, and immediately before dosing] on Day 8.) Three-point moving averages, over successive 10-minute intervals, were calculated for changes from baseline for BP and HR out to 6 hours postdose for each patient (excluding the orthostatic measurements) in each period. The maximum 3-point mean moving average change from baseline (MMACB) was calculated for each patient on Day 8 and Day 13 in each period. If the lower limit of the 90% CI for the least square mean difference of the MMACB for systolic and diastolic BP was greater than -10 or -8 mm Hg, respectively, then it was concluded that fosaprepitant IV or oral aprepitant given concurrently with diltiazem does not result in a clinically significant decrease in systolic or diastolic blood pressure beyond those changes induced by diltiazem alone.

RESULTS

Pharmacokinetics:

Aprepitant PK:

Day 8 data: Comparing the AUC_{0-24 hr} following dosing of fosaprepitant IV 100 mg with and without diltiazem, the geometric mean AUC_{0-24 hr} ratio (with diltiazem/without diltiazem) and 90% confidence interval were 1.45 (1.17, 1.79), (p=0.017).

Day 13 data: Comparing the AUC_{0-24 hr} following dosing of oral aprepitant 300 mg Formulation B (Phase IIa tablet administered 30 minutes after breakfast) daily for 5 days with and without diltiazem, the geometric mean AUC_{0-24 hr} ratio (with diltiazem/ without diltiazem) and 90% confidence interval were 2.00 (1.50, 2.66), (p=0.005).

Diltiazem and its metabolites:

Day 8 data: Comparing the AUC_{0-24 hr} of diltiazem, desacetyldiltiazem, and N-desmethyl-diltiazem following dosing of diltiazem with and without fosaprepitant IV, the geometric mean AUC_{0-24 hr} ratio (with fosaprepitant/without fosaprepitant) and 90% confidence interval were 1.40 (1.23, 1.58), (p=0.001); 1.35 (1.18, 1.55), (p= 0.004); and 1.11 (1.05, 1.18) (p=0.011), respectively.

Day 13 data: Comparing the AUC0-24 hr of diltiazem, desacetyldiltiazem, and N-desmethyl diltiazem following dosing of diltiazem with and without oral aprepitant, the geometric mean AUC0-24 hr ratio (with fosaprepitant/without fosaprepitant) and 90% confidence interval were 1.66 (1.44, 1.92), (p<0.001); 2.14 (1.80, 2.55), (p<0.001); and 0.91 (0.76, 1.09), (p=0.338), respectively.

Pharmacodynamics:

Pharmacodynamic results are presented in the order in which the study was conducted. That is, pharmacodynamic results following no medication and dosing of fosaprepitant IV/aprepitant PO or placebo alone are presented first; results following dosing of diltiazem and L-758298/MK-0869 or diltiazem and placebo are presented second.

Table: Pharmacodynamic Parameters Following No Medication or IV L-758298 (fosaprepitant) in Period 1 (N=8)

	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: Pharmacodynamic Parameters Following No Medication or Oral MK-0869 in Period 1 (N=8)

	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: Pharmacodynamic Parameters Following Diltiazem With or Without L-758298 (Fosaprepitant IV) in Periods 2 and 3 (N=9)

	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: Pharmacodynamic Parameters Following Diltiazem With or Without MK-0869 in Periods 2 and 3 (N=9)

	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					

Safety:

- Five patients had clinical adverse experiences; none were considered serious. Two patients had clinical adverse experiences that were considered possibly drug related by the investigator. No patients discontinued due to clinical adverse experiences.
- Two patients had laboratory adverse experiences; none were considered drug related, though one of these (allocation number [AN] 1604) had serious laboratory adverse experiences and discontinued due to them. AN 1604 had serious laboratory adverse experiences of active hepatitis C virus, alkaline phosphatase increased, alanine aminotransferase increased, and aspartate aminotransferase increased, and discontinued therapy prior to dosing Day 12 of Period 3, after having been administered 120 mg diltiazem 3 times daily and 300 mg of MK-0869 once daily.
- Two patients had other (ECG) adverse experiences; none were considered serious. One of these patients (AN 1601) had 4 other (ECG) adverse experiences that were considered

possibly drug related (2 on diltiazem alone, 1 on diltiazem and L-758298, and 1 on diltiazem and MK-0869). The second patient (AN 1707) discontinued due to an other (ECG) adverse experience: a prolonged PR interval/1st degree AV block that was considered by the investigator to be probably not drug related. This adverse experience occurred on Day 7 of Period 2, while the patient was on diltiazem but before the patient received either L-758298 or matching placebo IV.

- There were no deaths reported for this study.

REVIEWER'S COMMENTS:

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)

Appendix 2: Cover Sheet and OCP Filing/Review Form

<i>Office of Clinical Pharmacology</i>				
<i>New Drug Application Filing and Review Form</i>				
General Information About the Submission				
	Information		Information	
NDA Number	22-023	Brand Name		
OCP Division (I, II, III)	III	Generic Name	Fosaprepitant Dimeglumine	
Medical Division	Division of Gastroenterology Products	Drug Class	NK1-receptor antagonist	
OCP Reviewer	Sue-Chih Lee, Ph.D.	Indication(s)	Prevention of chemotherapy-induced nausea and vomiting	
OCP Deputy Division Director	Hae-Young Ahn, Ph.D.	Dosage Form	Injection	
Date of Submission	3/31/06 7/28/06 2/12/07	Proposed Dosing Regimen	Single 115 mg administered 30 min prior to chemotherapy (as a substitute for oral Emend 125 mg) on Day 1 only	
Estimated Due Date of OCP Review	April 18, 2007	Route of Administration	IV	
Medical Division Due Date	April 18, 2007	Sponsor	Merck	
PDUFA Due Date	May 3, 2007	Priority Classification	Standard	
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
Clinical Pharmacology				
Mass balance:	X	2	2	
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)-				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vivo effects of primary drug:	X	2	2	
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				

Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X	1	1	
solution as reference:				
alternate formulation as reference:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
QT study	X	1		Reviewed by QT-IRT
Simulations				
Reference Articles	X	2	2	
Total Number of Studies			4	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Does the relative bioavailability of IV fosaprepitant 115 mg compared to oral aprepitant 125 mg support the efficacy of IV fosaprepitant?			
Other comments or information not included above				
Primary reviewer Signature and Date	Sue-Chih Lee, Ph.D. 4/21/07			
Secondary reviewer Signature and Date	Hae-Young Ahn, Ph.D.			

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

/s/

Sue Chih Lee
4/30/2007 04:34:08 PM
BIOPHARMACEUTICS

Hae-Young Ahn
4/30/2007 04:52:20 PM
BIOPHARMACEUTICS

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

DATE: December 8, 2006

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 12/11/06
Associate Director – Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-023,
Fosaprepitant Dimeglumine Injection, 100 mg, 115 mg,
Sponsored by Merck & Co., Inc.

TO: Brian Harvey, M.D., Ph.D.
Director,
Division of Gastroenterology Products (DGP)

At the request of DGP, the Division of Scientific Investigations (DSI) conducted an audit of Part V of the following clinical trial.

Protocol #12: A Randomized, 5-part, Intravenous Study of the Safety, Tolerability, Bioequivalence, and Drug Interaction Potential of the Final Market Image Formulations of L-758,298 in Young Healthy Subjects.

The clinical portion of Protocol #12 was conducted at _____
_____. The analytical portion of Protocol # 12 was conducted
at Merck Research Laboratories, Department of Drug Metabolism, West Point, PA. Following the inspection of the clinical (10/30/06 - 11/3/06) and analytical (10/10/06 - 10/13/06) portions of Protocol 12 Part V, no significant issues were found and no Form FDA 483 was issued to _____ and Merck Research Laboratories. However, please be aware that _____ was closed as a phase I clinic study unit on July 17, 2006 and the FDA inspection was conducted at _____ which is a temporary office set up by _____ to cover their wind down financial activities and FDA inspections until March 2007. During the review of the source documents, the FDA investigator found that several ECG reports from study subjects were changed from 'abnormal' to 'normal' by the site's medical doctor during the review of these reports. The site explained that these changes were necessary due to errors made by the ECG interpretation machine. In light of this observation and the previous complaints regarding _____, DSI

b(4)

b(4)

is of the opinion that these ECG reports (Attachment 1) be subjected to further review by the Medical Officer in the Review Division.

Conclusion:

DSI recommends that the data from Protocol #12 Part V be accepted for review. The Medical Officer in the Review Division should review the ECG reports provided in Attachment 1 and confirm that the ECGs in these reports are normal.

After you have reviewed this transmittal memo, please append it to the original NDA submissions.

Martin K. Yau 12/8/06
Martin K. Yau, Ph.D.

Final Classifications for Inspection Concerning NDA 22-023 Protocol #12 Part V:

NAI - Merck Research Laboratories, Department of Drug Metabolism, West Point, PA.
NAI - _____

b(4)

cc:

HFD-45/RF

HFD-48/Yau(2)/Himaya/CF

DGP/Scroggs/NDA 22-023

HFR-CE100/Rashti

HFR-SE2575/ Menendez

Drafted: MKY/12/8/06

FACTS: 747839

DSI:5710; O:\BE\circover\21023merck.fos.doc

Attachment I

15 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

X Personal Privacy (b6)

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

/s/

Amalia Himaya
12/11/2006 12:54:04 PM
CSO