

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-337**

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

## CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

---

NDA: 21-337  
SUBMISSION DATE: 11/30/00  
PRODUCT: Ertapenem Sodium 1 gram  
TRADE NAME: Invanz® IV/IM  
DOSAGE FORM: Sterile lyophilized powder  
SPONSOR: Merck & Co., Inc.  
West Point, PA 19486  
TYPE OF SUBMISSION: Original NME  
REVIEWER: Charles Bonapace, Pharm.D.  
TEAM LEADER: Frank Pelsor, Pharm.D.

---

### SYNOPSIS

The sponsor submitted original NDA 21-337 for MK-0826 (ertapenem sodium, L-749345), a new 1- $\beta$ -methyl carbapenem for the treatment of complicated intra-abdominal infections, acute pelvic infections, complicated skin and skin structure infections, community-acquired pneumonia, and complicated urinary tract infections, including pyelonephritis. The proposed dosage regimen of MK-0826 is 1 g IV or IM once daily.

---

#### **Dose proportionality:**

MK-0826 exhibits nonlinear pharmacokinetics within the therapeutic dosing range. Unbound MK-0826 AUCs increased greater-than dose proportional, whereas total MK-0826 AUCs increased less-than dose proportional following single IV doses ranging from 0.25 g to 3 g IV.

#### **Absolute bioavailability:**

The absolute bioavailability of a single 1 g dose of MK-0826 administered IM is 90% (90% confidence interval 0.870 to 0.934) compared to 1 g administered IV.

#### **Distribution:**

The mean volume of distribution of unbound MK-0826 ranged from 1.75 to 1.95 L/kg, whereas the volume of distribution of total MK-0826 ranged from 0.11 to 0.12 L/kg.

MK-0826 is approximately 94% protein bound, primarily to albumin. Two classes of binding sites have been identified, of which the tighter binding site likely represents a single binding site on albumin. Thus, MK-0826 illustrates concentration-dependent protein binding within the therapeutic range. Differences in the extent of protein binding have also been observed between male and female subjects as well as between young and elderly subjects.

#### **Metabolism and elimination:**

The primary mechanism of elimination is glomerular filtration and active transport into the proximal tubule of the kidney. Approximately 80% of an administered dose is excreted in the urine, half of which is metabolized by dihydropeptidase-1 in the renal tubules to the inactive ring-opened metabolite L-774183.

**Special populations:**

Following a single 1 g IV dose of MK-0826 in patients with advanced renal impairment, the  $AUC_{0-\infty}$  of total MK-0826 increased 200% whereas the  $AUC_{0-\infty}$  of unbound MK-0826 increased 335%. Compared to healthy young subjects, the plasma clearance in subjects with advanced renal impairment was decreased by 67% and 77% for total and unbound MK-0826, respectively.

Age was shown to significantly impact the pharmacokinetics of MK-0826. Following the administration of 1 g IV, the renal clearance in elderly healthy subjects (65 years or older) was only 68% of young healthy subjects. Consequently, elderly subjects were associated with a 37% increase in total  $AUC_{0-\infty}$  and 67% increase in unbound  $AUC_{0-\infty}$  compared to young subjects. The increased exposure of elderly subjects was associated with a reduction in creatinine clearance.

**Drug interactions:**

MK-0826 appears to be neither a substrate nor inhibitor of CYP P450 isozymes (1A2, 2C9, 2C19, 2D6, 2E1, 3A4) and p-glycoprotein at concentrations approximately equivalent to a single 2 g IV dose.

A modest increase in MK-0826 plasma exposure measures ( $AUC$  and concentration at the end of infusion,  $C_{\text{eoi}}$ ) were observed when co-administered with probenecid. Probenecid 500 mg q6h for three days increased the  $AUC_{0-\infty}$  and  $C_{\text{eoi}}$  of a single 1 g IV dose of MK-0826 by 73% and 37%, respectively.

The sponsor also evaluated the effect of MK-0826 on the protein binding of warfarin. Plasma concentrations of total MK-826 equivalent to a 1 g dose IV resulted in a transient 8% to 9% increase in the unbound concentration of warfarin *in vitro*.

**Pharmacokinetic/pharmacodynamic relationship:**

The sponsor characterized the pharmacodynamic activity of MK-0826 using *in vivo* animal models against a variety of pathogens to determine the pharmacodynamic parameter most associated with efficacy of MK-0826. Consistent with other  $\beta$ -lactam antibiotics, the pharmacodynamic parameter associated with efficacy was the percentage of the dosing interval in which the plasma concentration remained above the MIC (%T > MIC). The minimal %T > MIC associated with efficacy in *in vivo* models varied by organism, but ranged from          (*S. pneumoniae*) to          (*S. aureus*) for total MK-0826 concentrations and          (*S. pneumoniae*) to          (*S. aureus*) for unbound MK-0826 concentrations.

**RECOMMENDATION:**

This application was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation III and found to be acceptable from a clinical pharmacology point of view.

\_\_\_\_\_  
Charles R. Bonapace, Pharm.D.  
Office of Clinical Pharmacology/Biopharmaceutics  
Division of Pharmaceutical Evaluation III

RD/FT initialed by Frank. Pelsor, Pharm.D., Team Leader \_\_\_\_\_

cc:  
Division File: NDA 21-337  
HFD-520 (CSO/Dillon-Parker)  
HFD-880 (Division File, Pelsor, Lazor, Bonapace)

**APPEARS THIS WAY  
ON ORIGINAL**

---

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

## TABLE OF CONTENTS

	Page Number
Synopsis.....	1
Recommendation.....	2
Table of Contents.....	4
Background.....	5
Indications.....	5
Proposed Dosage and Administration.....	6
Chemistry.....	6
Assay methodology.....	6
Mechanism of Action.....	6
Exposure-Response Relationship.....	7
Dose Selection.....	7
Protein Binding.....	8
<b>IV Administration</b>	
Single Dose Pharmacokinetics.....	9
Multiple Dose Pharmacokinetics.....	14
<b>IM Administration</b>	
Single Dose Pharmacokinetics.....	16
Multiple Dose Pharmacokinetics.....	17
Pharmacodynamics (IM vs. IV administration).....	18
<b>Absolute Bioavailability.....</b>	<b>19</b>
<b>Drug Metabolism.....</b>	<b>19</b>
<b>Drug Interactions</b>	
Cytochrome P450.....	21
P-Glycoprotein.....	22
Probenecid.....	22
Warfarin.....	24
<b>Special Populations</b>	
Renal Impairment.....	25
Elderly.....	31
<b>Tissue Distribution.....</b>	<b>36</b>
<b>Transfer into Breast Milk.....</b>	<b>37</b>
<b>Labeling.....</b>	<b>41</b>

## BACKGROUND

MK-0826 (ertapenem sodium, L-749345), a 1- $\beta$ -methyl carbapenem, is a new member of the  $\beta$ -lactam class of antimicrobials. Like other  $\beta$ -lactam antibiotics, MK-0826 blocks bacterial cell-wall synthesis by binding to specific penicillin binding proteins and is rapidly bactericidal. Carbapenems with a hydroxyethyl side chain at C6 are resistant to  $\beta$ -lactamases, including extended spectrum  $\beta$ -lactamases. The structure of MK-0826 is shown in Figure 1.

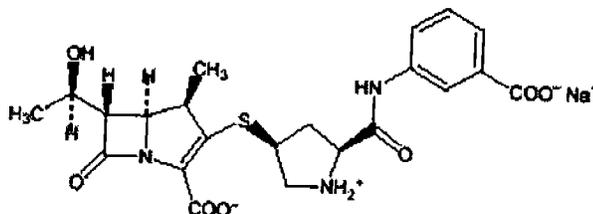


Figure 1

Ertapenem has in vitro activity against most common aerobic and anaerobic Gram-positive and Gram-negative pathogens including *Streptococcus* species, methicillin-susceptible staphylococci, *Enterobacteriaceae*, and most anaerobic species. In addition, it has in vitro activity against penicillin-resistant (penicillin minimum inhibitory concentration [MIC]  $\geq 2$   $\mu\text{g/mL}$  *Streptococcus pneumoniae* (PRSP) and against gram-negative enterics carrying plasmid- or chromosomally-mediated  $\beta$ -lactamases, including the extended-spectrum  $\beta$ -lactamases (ESBLs) and amp C  $\beta$ -lactamases. Ertapenem has limited activity against methicillin-resistant Staphylococci, Enterococci, *Corynebacteria jeikeium*, *Pseudomonas* species, *Acinetobacter* species, *Aeromonas hydrophilia*, *Burkholderia cepacia*, *Lactobacillus* species, *Stenotrophomonas maltophilia*, *Bacteroides distasonis*, and *Clostridium difficile*.

## INDICATIONS

The sponsor seeks approval of MK-0826 for the treatment of complicated intra-abdominal infections, acute pelvic infections, complicated skin and skin structure infections, community-acquired pneumonia, and complicated urinary tract infections, including pyelonephritis.

The Phase IIb/III clinical development program was comprised of a total of 7 (5 pivotal and 2 supportive) large clinical efficacy protocols in support of 5 infectious disease indications, which enrolled a total of 3333 patients (1783 randomized to treated with ertapenem). The standard dose of ertapenem studied in all of the Phase IIb/III clinical trials was 1 g administered parenterally (IV) once daily.

Additionally, the study design in the complicated urinary tract infection studies and community acquired pneumonia studies allowed an optional switch to an appropriate oral antimicrobial after a minimum of 3 days of parenteral treatment, provided specific clinical response criteria were met and clinical improvement was clearly demonstrated. In the remaining 3 indications, where switching to an oral agent is less commonly practiced, the protocol design permitted IV therapy only.

## PROPOSED DOSAGE AND ADMINISTRATION

The recommended treatment regimen of MK-0826 is 1 gram IV or IM once-daily for all indications with the length of therapy ranging from 3 to 14 days.

MK-0826 is supplied as a sterile lyophilized powder for dilution prior to intravenous infusion or intramuscular injection. Each 20 mL vial contains ertapenem sodium (1 gram/vial of ertapenem as the free acid) in a lyophilized matrix prepared from a bicarbonate buffer solution adjusted to pH 7.5.

Ingredient	Pre-Lyophilization Solution mg/1 gram vial
Ertapenem sodium (equivalent free acid)	_____
Sodium bicarbonate USP	_____
Sodium hydroxide NF	_____
Water for injection USP <sup>†</sup>	_____

<sup>†</sup> Water is removed during lyophilization

## CHEMISTRY

### CLINICAL PHARMACOLOGY

**Q. Are the assay methodologies used to quantitate MK-0826 concentrations acceptable?**

The sponsor developed \_\_\_\_\_ with UV detection and microbiological methods to quantitate MK-0826 concentrations in plasma (total and unbound), whole blood, urine, dialysate fluid, breast milk, and skin blister fluid. The accuracy and precision of the methods were within  $\pm 15\%$  and were found acceptable. The specificity was acceptable in all the matrices analyzed.

The stability of MK-0826 was evaluated in whole blood, plasma (total and unbound), urine, dialysate fluid, breast milk, and skin blister fluid. In plasma, stability was assessed under the following conditions:

MK-0826 was shown to be stable in urine, dialysate fluid, breast milk, and skin blister fluid. However, the stability of MK-0826 in whole blood placed on ice (\_\_\_\_\_) may allow up to \_\_\_\_\_ degradation prior to quantitation of MK-0826 concentrations.

**Q. What is the mechanism of action for MK-0826?**

Penicillin-binding proteins (PBPs) play an essential role in the biosynthesis of bacterial cell wall peptidoglycan and are the primary targets of  $\beta$ -lactam antibiotics. Ertapenem blocks bacterial cell-wall

synthesis by binding to specific PBPs. In competitive binding studies with *Escherichia coli*, ertapenem binds strongly to PBPs 1a, 1b, 2, 3, 4, and 5, displaying highest affinity for PBP2 and PBP3. Microscopic examination of *E. coli* exposed to sub-minimum inhibitory concentrations (MIC) demonstrated morphologic changes consistent with inhibition of PBP2 and PBP3.

**Q. Has the exposure-response relationship been studied?**

The sponsor performed *in vitro* susceptibility studies and *in vivo* pharmacodynamic animal models to describe the dose-response relationship of MK-0826. Consistent with previous  $\beta$ -lactam antibiotics, dosing frequency was found to be an important determinant of *in vivo* efficacy. The total daily dose required for bacteriostatic effects was lower with more frequent dosing. Thus, the frequency of the dosing interval influences the efficacy of ertapenem.

A neutropenic murine thigh infection model was used to determine if the %T >MIC required to produce a net bacteriostatic effect was similar for various pathogens. The activity of MK-0826 was evaluated against 9 strains of gram-negative bacilli, 3 strains of *S. aureus*, and 11 strains of *S. pneumoniae* by dosing every 12 hours for one day. The mean %T >MIC required for a bacteriostatic effect (no net growth or killing compared to the initial inoculum) in this model was 34.5% for total drug (16.5% for free drug) for gram-negative bacilli, 43% for total drug (24.7% for free drug) for *S. aureus*, and 24.2% for total drug (6.2% for free drug) for *S. pneumoniae*. In general, *S. pneumoniae* isolates required a smaller percentage of time above the MIC for a bacteriostatic effect than other organisms.

~~Another murine animal model study used immunocompetent mice inoculated with 160-200 LD<sub>50</sub> of penicillin-resistant *S. pneumoniae*. Three different strains of penicillin-resistant *S. pneumoniae* were studied. MK-0826 (5 mg/kg + cilastatin or 20 mg/kg + cilastatin) was administered as a single dose. An average of 2.3 and 3.3 hours above the MIC was required to achieve the ED<sub>50</sub> or ED<sub>100</sub>, respectively.~~

Due to differences in pharmacokinetics, immune function (neutropenic thigh infection model), and the dosing regimen between animal models and humans, the minimum %T >MIC associated with efficacy in humans cannot be concluded. However, the results from *in vivo* animal studies and pharmacokinetic study P001 provide evidence for the efficacy of MK-0826 based on unbound concentrations.

**Q. How was the 1 gram dose selected?**

The human pharmacokinetic data in conjunction with the *in vitro* activity of ertapenem against a broad range of relevant pathogens predicts that 1 g IV once daily will effectively treat most bacterial pathogens excluding *Pseudomonas* species, *Acinetobacter* species, *Enterococcus* species, and methicillin-resistant *Staphylococcus aureus*.

In pharmacokinetic study P001, the sponsor determined the duration of which the plasma concentration of total MK-0826 was greater than 15  $\mu$ g/mL (the postulated bactericidal plasma concentration) following administration of 1 g IV in healthy male (n=6) and female (n=6) volunteers. The mean total plasma concentration at 12 hrs (C12) and the mean time over which the total plasma concentration was equal to 15  $\mu$ g/mL (T15) are shown in the table below.

	Mean	90% CI
<b>Males</b>		
C12 ( $\mu$ g/mL)	12.06 $\pm$ 3.55	(9.14, 14.97)
T15 (hr)	10.83 $\pm$ 1.33	(9.74, 11.92)
<b>Females</b>		
C12 ( $\mu$ g/mL)	8.30 $\pm$ 1.20	(7.31, 9.28)
T15 (hr)	9.48 $\pm$ 0.62	(8.97, 9.99)

The upper limit of the 90% CI for C12 did not include 15 µg/mL for males or females, a goal concentration that was considered adequate to treat relevant organisms. Based on the data above, the %T >MIC for unbound MK-0826 concentrations would be less than 50% for organisms with MICs ≥ 1.0. However, in vivo animal studies demonstrated that %T >MIC of 25% (based on unbound concentrations) were associated with efficacy and support empiric investigation of the 1 g daily dosage regimen of MK-0826 in patients with infections.

**Q. Why doesn't MK-0826 need to be administered with cilastatin?**

The β-lactam ring of carbapenems are metabolized by human renal dehydropeptidase-1 (DHP-1) to the ring-opened metabolite within the kidney. The 1-β-methyl group of MK-0826 confers stability against DHP-1; thus MK-0826 does not require the co-administration of cilastatin to maintain adequate urinary concentrations. MK-0826 was found to be hydrolyzed at approximately 0.25 times the rate of imipenem versus hog DHP-1 and 0.77 times the rate of imipenem versus mouse DHP-1. The improved resistance of MK-0826 to DHP-1 renal enzyme action allows administration of ertapenem as a single entity.

**Q. What is the relationship between MK-0826 concentration and the fraction unbound?**

The unbound fraction of MK-0826 following the administration of 0.5 g to 3 g MK-0826 in male and female subjects was determined in study P009. In this study, MK-0826 was administered IV over 30 minutes, except for the 3 g dose, which was administered over 120 minutes. The mean fraction of unbound MK-0826 increased with increasing dose administered (except for the 3 g dose due to the increased duration of infusion). In addition, females were usually associated with a similar or greater unbound fraction than males at all sample times for doses ranging from 0.5 g to 3 g.

**Fraction unbound of MK-0826 at various time points for the 0.5 g, 1 g, 2 g, and 3 g doses**

Gender	Time (hr)											
	0	0.25	0.5	0.75	1	1.5	2	4	6	8	12	18
<b>Dose = 0.5 g</b>												
Male	0	0.05	0.06	0.06	0.05	0.06	0.05	0.05	0.05	0.05	0.04	0.06
Female	0	0.06	0.07	0.06	0.06	0.06	0.06	0.05	0.05	0.05	0.04	0.06
Overall	0	0.05	0.06	0.06	0.06	0.06	0.05	0.05	0.05	0.05	0.04	BLQ*
<b>Dose = 1 g</b>												
Male	0	0.06	0.08	0.06	0.06	0.06	0.05	0.05	0.05	0.05	0.04	0.06
Female	0	0.07	0.09	0.08	0.07	0.07	0.07	0.05	0.05	0.05	0.04	0.06
Overall	0	0.07	0.08	0.07	0.07	0.07	0.06	0.05	0.05	0.05	0.04	0.04
<b>Dose = 2 g</b>												
Male	0	0.09	0.13	0.12	0.09	0.08	0.07	0.06	0.05	0.05	0.04	0.05
Female	0	0.10	0.18	0.12	0.11	0.09	0.08	0.06	0.05	0.06	0.04	0.05
Overall	0	0.10	0.15	0.12	0.10	0.09	0.08	0.06	0.05	0.05	0.04	0.04
<b>Dose = 3 g (120 min infusion)</b>												
Male	0	0.07	0.07	0.08	0.09	0.12	0.13	0.08	0.06	0.06	0.05	0.05
Female	0	0.06	0.08	0.10	0.11	0.14	0.15	0.08	0.06	0.06	0.05	0.05
Overall	0	0.06	0.08	0.09	0.10	0.13	0.14	0.08	0.06	0.06	0.05	0.05

\*BLQ = below lower limit of quantitation

Since the plasma clearance of drugs with a low extraction ratio is proportional to the fraction unbound, the plasma clearance and renal clearance of MK-0826 is dependent upon the plasma concentration and thus the administered dose.

**Q. What are the pharmacokinetic characteristics of IV MK-0826? Are they linear within the therapeutic range?**

**Single dose pharmacokinetics**

The sponsor conducted a 2-part, double-blind, placebo-controlled study (P001) in healthy men (n=16) and women (n=8) to determine the pharmacokinetic profile of MK-0826 after single and multiple dose IV infusions. Subjects in each panel received all three doses. There was at least a 7-day washout between re-treatment within a panel. All doses were infused in a volume of 50 mL given over 30 minutes except the 3 g dose, which was administered in a volume of 100 mL over 60 minutes (increased to 120 minutes). The pharmacokinetic parameters from Part I (single dose) are summarized below.

**Arithmetic mean (SD) plasma and urine pharmacokinetic parameters following administration of a single IV dose of MK-0826 in men and women (based on total MK-0826 concentrations)**

Parameter	Panel A (Men)			Panel B (Men)			Women
	0.25 g	1.0 g	2.0 g	0.5 g	1.5 g	3.0 g	
Dose (g)							
AUC <sub>0-∞</sub> (μg*hr/mL)	172.0 (35.2)	588.7 (107.0)	1019.6 (180.0)	271.7 (42.2)	719.3 (84.9)	1228.7 (192.5)	563.2 (36.8)
Plasma clearance (mL/min)	24.9 (4.3)	29.0 (4.8)	33.4 (5.0)	31.3 (4.7)	35.2 (4.1)	41.6 (6.4)	29.7 (1.8)
Plasma clearance (mL/min/kg)	0.32 (0.05)	0.38 (0.06)	0.43 (0.06)	0.41 (0.07)	0.46 (0.06)	0.54 (0.08)	0.46 (0.06)
Half-life (hrs)*	4.59	4.64	4.43	4.47	4.42	4.34	3.64
Renal clearance (mL/min)	11.0 (2.3)	10.2 (1.8)	12.7 (3.4)	9.3 (1.2)	11.0 (1.9)	12.5 (2.7)	12.8 (1.3)
U48 (mg)	103.8 (30.5)	367.8 (81.8)	756.0 (182.3)	148.8 (14.2)	466.5 (90.5)	903.7 (158.7)	421.4 (28.3)
f <sub>e0-48</sub> (fraction)	0.41 (0.12)	0.36 (0.08)	0.39 (0.12)	0.30 (0.03)	0.31 (0.07)	0.30 (0.07)	0.43 (0.03)

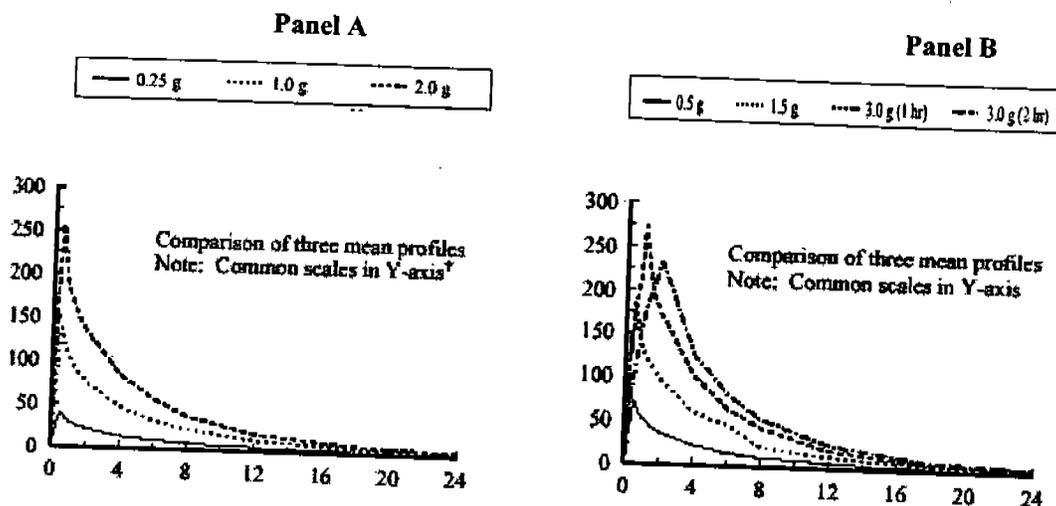
\* Harmonic mean

The AUC<sub>0-∞</sub> increased less than dose proportional and the plasma clearance and renal clearance increased with increasing dose. However, the fraction of the dose excreted unchanged in the urine remained approximately constant.

Male subjects in panel B had a greater plasma clearance than male subjects in Panel A and a smaller fraction of Mk-0826 excreted unchanged in the urine. The difference between the two panels could not be explained based on demographics.

**APPEARS THIS WAY  
ON ORIGINAL**

**Mean plasma concentration-time profiles of total MK-0826 following single IV doses to healthy male subjects**



The dose-adjusted  $AUC_{0-\infty}$  (based on the 1 g and 1.5 g dose in Panel A and Panel B, respectively) increased less than dose proportional for Panel A and Panel B (table below). However, the 90% CIs for the dose-adjusted AUCs were within 0.80 and 1.25.

**Geometric mean ratios of total MK-0826 plasma  $AUC_{0-\infty}$  following single IV doses in men**

Panel	Dose	N	Geometric mean $AUC_{0-\infty}$	Dose-adjusted geometric mean $AUC_{0-\infty}$	Dose-adjusted $AUC_{0-\infty}$ GMR	90% CI Dose-adjusted $AUC_{0-\infty}$ GMR
A	0.25 g	5	165.55	662.20	1.14	(1.07 - 1.21)
	1 g	6	581.16	581.16	--	--
	2 g	6	1007.90	503.95	0.87	(0.82 - 0.92)
B	0.5 g	6	269.08	807.24	1.13	(1.07 - 1.19)
	1.5 g	6	715.21	715.21	--	--
	3 g	6	1216.24	608.12	0.85	(0.81 - 0.90)

The sponsor also conducted an open-label, randomized, 4-period, crossover study (P009) in 16 healthy subjects (8 male and 8 female) to obtain pharmacokinetic information on total and unbound MK-0826 concentrations following single IV doses. There was at least a 7-day washout interval between periods. All doses were infused in 50 mL over 30 minutes except the 3 g dose, which was infused in 150 mL over 120 minutes. The total and unbound MK-0826 pharmacokinetic parameters are summarized in the tables below.

Arithmetic mean (SD) pharmacokinetic parameters of unbound MK-0826 in male and female subjects

Dose (g)	0.5 g	1 g	2 g	3 g
<b>AUC<sub>0-∞</sub> (µg*hr/mL)</b>				
All	15.8 (2.3)	33.2 (5.5)	76.6 (13.2)	124.7 (24.6)
Male	15.1 (2.8)	31.6 (6.9)	69.0 (4.3)	114.5 (28.5)
Female	16.5 (1.3)	34.9 (3.2)	84.3 (5.8)	135.0 (15.7)
<b>C<sub>∞</sub> (µg/mL)</b>				
All	5.29 (1.2)	12.9 (3.2)	43.3 (14.8)	39.4 (10.6)
Male	4.6 (1.1)	11.1 (3.2)	34.4 (12.9)	34.6 (12.5)
Female	6.0 (0.9)	14.8 (2.0)	52.3 (10.8)	44.1 (5.8)
<b>V<sub>ss</sub> (L)</b>				
All	138.1 (41.9)	123.1 (37.2)	--	--
Male	163.0 (45.3)	150.3 (33.1)	--	--
Female	113.3 (17.5)	96.0 (13.7)	--	--
<b>Plasma Clearance (mL/min)</b>				
All	539 (82)	514 (81)	451 (98)	417 (89)
Male	570 (103)	546 (99)	504 (116)	459 (105)
Female	507 (39)	481 (42)	397 (27)	375 (44)
<b>Renal Clearance (mL/min)</b>				
All	236 (64)	217 (68)	194 (51)	173 (51)
Male	205 (68)	183 (72)	175 (59)	162 (65)
Female	266 (47)	251 (45)	214 (34)	185 (31)

Arithmetic mean (SD) pharmacokinetic parameters of total MK-0826 in male and female subjects

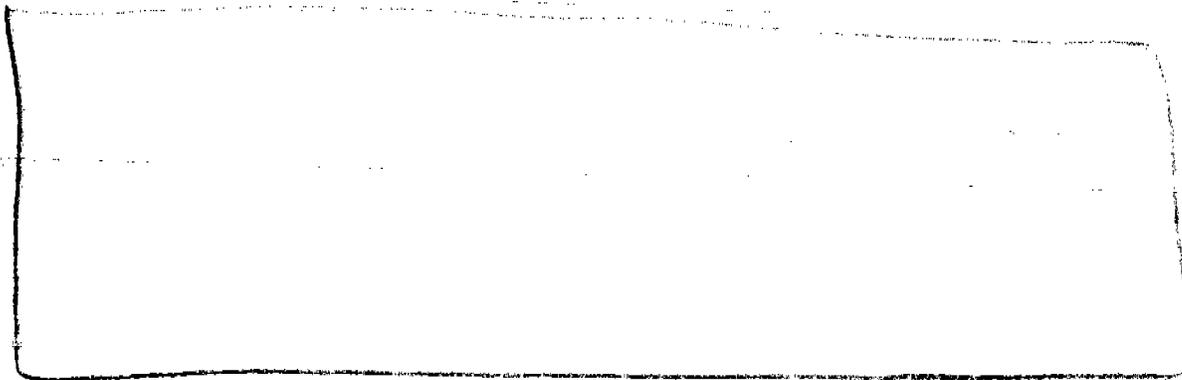
Dose (g)	0.5 g	1 g	2 g	3 g
<b>AUC<sub>0-∞</sub> (µg*hr/mL)</b>				
All	306 (37)	572 (69)	1011 (118)	1407 (230)
Male	299 (40)	575 (84)	986 (144)	1376 (302)
Female	312 (34)	569 (55)	1036 (87)	1438 (141)
<b>C<sub>∞</sub> (µg/mL)</b>				
All	83 (12)	155 (22)	283 (41)	274 (41)
Male	78 (13)	144 (21)	268 (48)	253 (48)
Female	88 (9)	166 (19)	298 (29)	296 (19)
<b>V<sub>ss</sub> (L)</b>				
All	7.82 (1.33)	8.21 (1.47)	--	--
Male	8.61 (1.29)	8.95 (1.57)	--	--
Female	7.03 (0.82)	7.48 (0.94)	--	--
<b>Plasma Clearance (mL/min)</b>				
All	27.6 (3.2)	29.5 (3.4)	33.4 (4.1)	36.3 (5.2)
Male	28.3 (3.7)	29.5 (4.1)	34.4 (4.9)	37.6 (6.5)
Female	27.0 (2.8)	29.5 (2.8)	32.4 (3.0)	35.1 (3.6)
<b>Renal Clearance (mL/min)</b>				
All	12.3 (3.7)	12.7 (4.2)	14.9 (4.6)	15.5 (4.9)
Male	10.3 (3.4)	9.8 (3.2)	12.2 (4.2)	13.5 (5.4)
Female	14.3 (3.0)	15.5 (2.9)	17.6 (3.3)	17.6 (3.7)
<b>Half-life (hrs)</b>				
All	3.79 (0.42)	3.86 (0.49)	3.81 (0.47)	3.66 (0.54)
Male	4.08 (0.30)	4.16 (0.34)	4.05 (0.45)	3.99 (0.45)
Female	3.51 (0.33)	3.56 (0.45)	3.56 (0.36)	3.33 (0.41)

	$Fe_{0-24}$ (% dose)			
	All	44.0 (13.2)	43.1 (14.7)	44.3 (13.3)
Male	35.4 (9.7)	33.7 (12.9)	34.8 (10.1)	35.2 (11.4)
Female	52.7 (10.5)	52.4 (9.9)	53.8 (8.4)	49.7 (9.1)

The plasma concentration-time profiles of total and unbound MK-0826 are shown below.

Total MK-0826

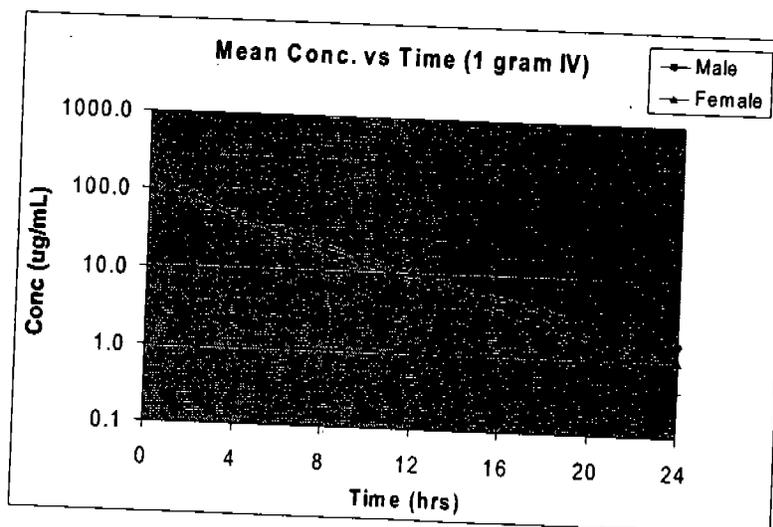
Unbound MK-0826



The mean plasma clearance and renal clearance of unbound MK-0826 decreased with increasing dose, whereas the plasma and renal clearances of total MK-0826 increased with increasing dose. Similar trends were observed across male and female subjects.

Differences were observed in the pharmacokinetic parameters between male and female subjects. Females were associated with a greater  $AUC_{0-\infty}$ ,  $C_{eoi}$ ,  $CL_R$ , and  $fe_{0-24}$ . Males were associated with a greater  $CL_T$ ,  $V_{ss}$ , and longer half-life. Statistically significant differences were noted for  $V_{ss}$  ( $p=0.051$ ),  $C_{eoi}$  ( $p=0.035$ ), half-life ( $p=0.020$ ), and  $fe_{0-24}$  ( $p<0.001$ ). When body weight was taken into consideration, it accounted for differences in  $V_{ss}$ ,  $C_{eoi}$ , and  $CL_T$  between genders.

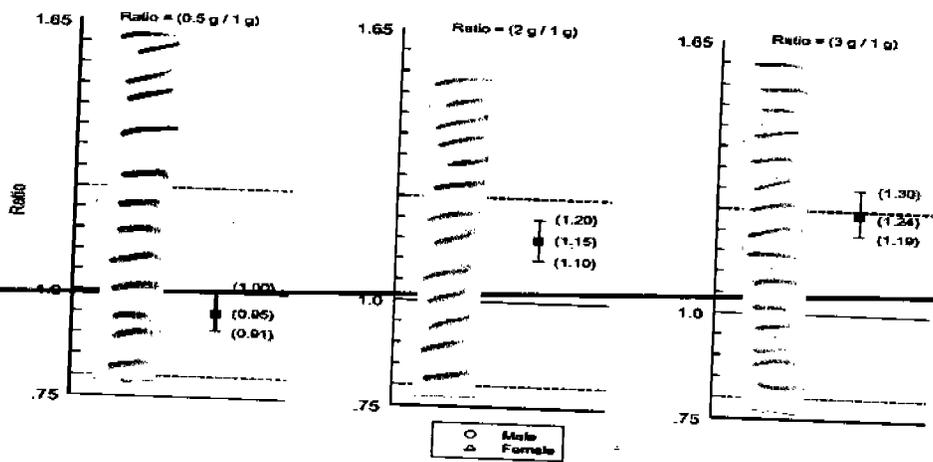
The total plasma concentration-time profile following the administration of 1 g IV in male and female subjects is shown below. As stated above, a greater  $C_{eoi}$  and faster rate of elimination was seen in female subjects.



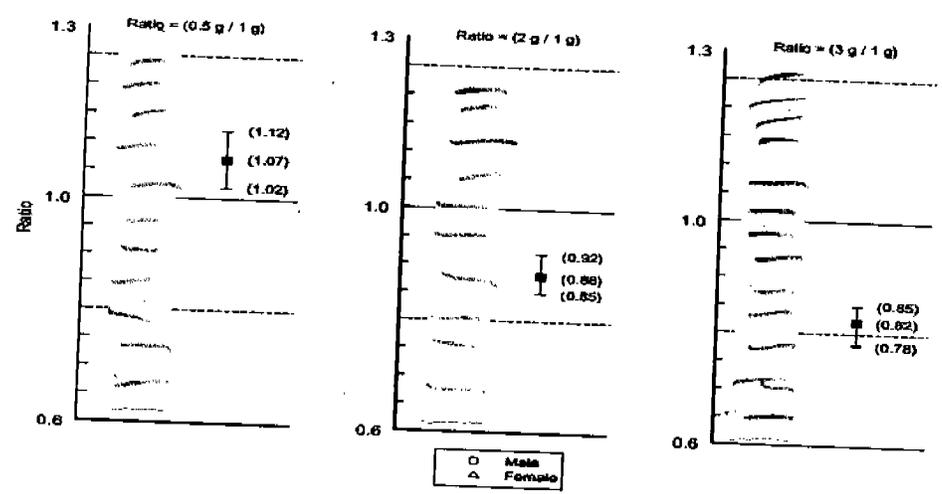
The  $AUC_{0-\infty}$  of unbound MK-0826 increased greater-than dose proportional, whereas the opposite was found with the  $AUC_{0-\infty}$  of total MK-0826 when doses were adjusted relative to the 1 g dose. The 90% confidence interval of the dose adjusted (to 1 g)  $AUC_{0-\infty}$  was within 0.8 to 1.25 for the 0.5 g and 2 g doses based on unbound and total MK-0826. The  $AUC_{0-\infty}$  was outside the 90% confidence interval for the 3 g dose based on unbound and total MK-0826.

The 90% confidence interval for the 3 g dose (compared to the 1 g dose) based on unbound  $AUC_{0-\infty}$  was outside the 90% confidence interval for males and females, but within the 90% confidence interval with females based on total  $AUC_{0-\infty}$ . The data is summarized in the figures below.

**Dose-adjusted  $AUC_{0-\infty}$  ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ ) ratios of unbound MK-0826 for individual subjects (open shapes) and AUC GMR with 90% CI for all subjects (solid squares)**



**Dose-adjusted  $AUC_{0-\infty}$  ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ ) ratios of total MK-0826 for individual subjects (open shapes) and AUC GMR with 90% CI for all subjects (solid squares)**



**Reviewer's comments:**

The pharmacokinetic non-linearity as the dosage increased from 0.25 g to 3 g is due to the concentration-dependent protein binding of MK-0826. Since MK-0826 is a low extraction ratio drug, the plasma

clearance of total MK-0826 decreased with increasing dose, whereas the plasma clearance of unbound MK-0826 increased with increasing dose.

The most commonly reported adverse effects in study P001 were nausea, headache, and diarrhea. Nausea was more frequently observed at the higher dose. During Part I, the first 2 patients in the 3 g dose group experienced nausea when MK-0826 was infused for 60 minutes. As a result, the infusion period was increased from 60 minutes to 120 minutes. No further patients experienced nausea in the 3 g dosing group.

The most commonly reported adverse reactions in study P009 following the administration of 0.5 g to 3 g MK-0826 were nausea, headache, and diarrhea. The incidence of nausea increased as the dose administered increased, whereas the incidence of headache and diarrhea was unaffected by the administered dose.

#### Comparison of adverse events by administered dose

Dose of MK-0826	Incidence of adverse effect		
	Nausea	Headache	Diarrhea
0.5 g (0.5 hr)	1/16	8/16	2/16
1 g (0.5 hr)	4/16	9/16	4/16
2 g (0.5 hr)	7/16	9/16	2/16
3 g (2 hr)	7/16	7/16	3/16

#### Multiple dose pharmacokinetics

The sponsor also addressed whether the pharmacokinetics of total MK-0826 following multiple doses can be predicted from single IV doses. Part 2 of study P001 consisted of 30 healthy men, of which 6 men were assigned to each dosage regimen. All doses were infused once daily in a volume of 50 mL given over 30 minutes except the 3 g dose, which was given in a volume of 100 mL over 120 minutes. The multiple-dose pharmacokinetic parameters are summarized below.

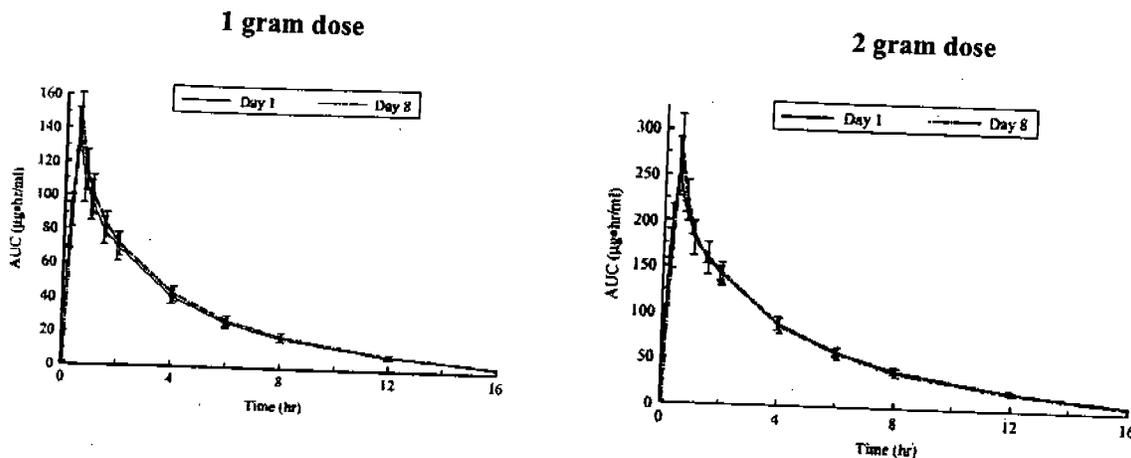
#### Arithmetic mean (SD) plasma and urine pharmacokinetic parameters following administration of multiple doses of MK-0826 on Day 1 and Day 8 in men

Parameter	Day 1					Day 8				
	0.25 g	0.5 g	1.0 g	2.0 g	3.0 g	0.25 g	0.5 g	1.0 g	2.0 g	3.0 g
AUC <sub>0-∞</sub> (μg*hr/mL)	152.2 (13.8)	292.2 (41.1)	489.2 (47.1)	1059.2 (51.4)	1575.8 (83.3)	--	--	--	--	--
AUC <sub>0-24</sub> (μg*hr/mL)	--	--	--	--	--	152.2 (16.7)	290.6 (43.7)	503.3 (46.8)	1024.2 (105.2)	1269.7 (102.8)
Half-life (hr)*	4.51	4.67	4.13	4.11	4.10	4.58	4.52	3.97	4.09	4.36
Plasma CL (mL/min)	27.5 (2.2)	29.0 (3.4)	34.2 (3.7)	31.2 (1.5)	31.8 (1.6)	27.5 (2.9)	29.2 (4.4)	33.5 (3.4)	32.8 (3.8)	39.7 (3.4)
Plasma CL (mL/min/kg)	0.33 (0.03)	0.36 (0.06)	0.43 (0.05)	0.40 (0.03)	0.40 (0.05)	0.33 (0.04)	0.36 (0.06)	0.42 (0.06)	0.42 (0.08)	0.50 (0.08)
Renal CL (mL/min)	9.5 (3.4)	9.4 (1.8)	9.5 (2.7)	11.5 (2.4)	12.2 (3.8)	9.3 (2.7)	9.6 (2.3)	10.2 (3.5)	13.3 (2.2)	13.0 (5.4)
f <sub>e0-24</sub> (fraction)	0.33 (0.11)	0.33 (0.05)	0.28 (0.08)	0.36 (0.08)	0.41 (0.12)	0.33 (0.08)	0.33 (0.08)	0.30 (0.10)	0.42 (0.06)	0.34 (0.14)

\* Harmonic mean

The multiple-dose pharmacokinetic parameters were similar across most doses between Day 1 and Day 8. The plasma clearance for the 3 g dose was greater on day 8 than day 1, resulting in a substantial decrease in the AUC<sub>0-24</sub> on Day 8 compared to the AUC<sub>0-∞</sub> on Day 1.

**Mean plasma concentration (µg/mL) of total MK-0826 (Day 1 and Day 8) following multiple 1 gram and 2 gram IV doses**



The plasma concentration-time profiles for the 1 g and 2 g doses between Day 1 and Day 8 were similar, as is reflected in the Day 8/Day 1 AUC geometric mean ratio below.

**Geometric mean ratios of total MK-0826 Day 8 AUC<sub>0-24</sub> versus Day 1 AUC<sub>0-∞</sub>**

Panel	Dose	N	Geometric mean AUC <sub>0-∞</sub> Day 1	Geometric mean AUC <sub>0-24</sub> Day 8	AUC GMR Day 8/Day 1	90% CI of AUC GMR
A	0.25 g	6	151.67	151.44	1.00	(0.95 - 1.04)
B*	0.5 g	5	290.13	288.00	0.99	(0.86 - 1.15)
C	1 g	6	487.18	501.44	1.03	(0.97 - 1.10)
D	2 g	6	1058.12	1019.30	0.96	(0.87 - 1.06)
E	3 g	6	1574.00	1266.06	0.80	(0.74 - 0.87)

\*Analysis excluding subject 38

The point estimates comparing Day 1 AUC<sub>0-24</sub> versus Day 8 AUC<sub>0-24</sub> were approximately 1.00 and the 90% confidence intervals were within 0.80 to 1.25 for all doses except for the 3 g dose. The point estimate for the 3 g dose was 0.80 and the 90% confidence interval ranged from 0.74 to 0.87. No accumulation of MK-0826 was observed between Day 1 and Day 8.

**Geometric mean ratios of total MK-0826 Day 1 AUC<sub>0-24</sub> versus Day 8 AUC<sub>0-24</sub>**

Panel	Dose	N	Geometric mean AUC <sub>0-24</sub> Day 1	Geometric mean AUC <sub>0-24</sub> Day 8	AUC GMR Day 8/Day 1	90% CI of AUC GMR
A	0.25 g	6	148.36	151.44	1.02	(0.97 - 1.07)
B*	0.5 g	5	283.25	288.00	1.02	(0.88 - 1.18)
C	1 g	6	480.70	501.44	1.04	(0.98 - 1.11)
D	2 g	6	1041.67	1019.30	0.98	(0.89 - 1.08)
E	3 g	6	1547.55	1266.06	0.82	(0.76 - 0.88)

**Reviewer comments:**

The multiple dose pharmacokinetic parameters from study P001 were based on total MK-0826 concentrations only. Multiple dose pharmacokinetic parameters of MK-0826 based on unbound drug concentrations have not been determined.

**Q. What are the pharmacokinetic characteristics of IM MK-0826?**

**Single dose IM pharmacokinetics**

The sponsor conducted a randomized, placebo-controlled, single-ascending-dose study (P011) in 11 healthy subjects (4 male and 7 female) to investigate the safety, tolerability, and pharmacokinetics of intramuscular MK-0826 following administration of 0.25, 0.5, and 1 g. Pharmacokinetic samples were only obtained following the 1 g dose. The comparison of pharmacokinetic parameters obtained from 1 g IM administration (n=11) to those obtained following 1 g IV administration (P009, n=16) are shown below.

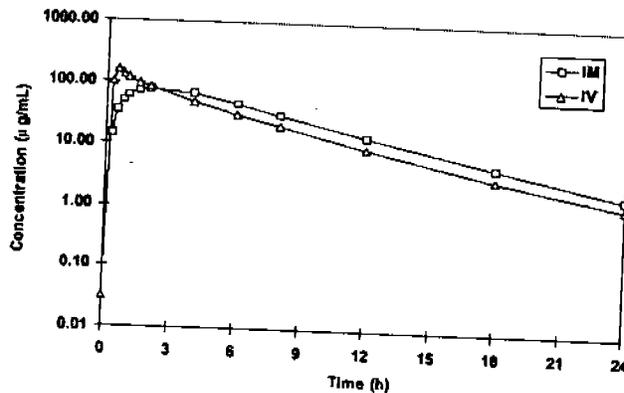
**Arithmetic mean pharmacokinetic parameters of total MK-0826 following the administration of 1 g IM and 1 g IV (study P009) to healthy male and female subjects**

	AUC <sub>0-∞</sub> (µg*hr/mL)	C <sub>max</sub> (µg/mL)	C <sub>∞</sub> (µg/mL)	T <sub>max</sub> (hrs)	Half-life* (hrs)
<b>1 g IM (study P011)</b>					
Mean	602.3	77.7	--	2.4	3.9
SD	107.3	13.5	--	1.0	0.5
Range					
<b>1 g IV (study P009)</b>					
Mean	572.1	--	154.9	--	3.9
SD	68.6	--	22.0	--	0.5
Range					

\* Harmonic mean

The plasma concentration-time profile of total MK-0826 comparing the administration of 1 g administered IM and IV is shown below.

**Mean plasma concentration-time profiles of total MK-0826 following a single 1 g IM dose with data from a single 1 g IV dose infused over 30 minutes (Protocol 009) in healthy young males and females**



The  $AUC_{0-\infty}$  of MK-0826 1 g IV infused over 30 minutes was less than the  $AUC_{0-\infty}$  following 1 g IM. The greater  $AUC_{0-\infty}$  with IM administration may be accounted for by differences in the subjects between the two studies. The mean body weight of subjects receiving 1 g IM (P011) was 64.8 kg, whereas subjects receiving 1 g IV (P009) was 69.6 kg.

Following IM administration, the  $T_{max}$  of MK-0826 was delayed by almost 2 hrs and the  $C_{max}$  was reduced by approximately 50%. However, three hrs following the administration of 1 g IM MK-0826, the plasma concentrations were similar between IM and IV administration.

**Reviewer comments:**

The sponsor compared the pharmacokinetics of MK-0826 following IM administration in study P011 to the pharmacokinetics following IV administration from a previous study (P009). Since the subjects enrolled in these two studies are different, the sponsor conducted study P019 to determine the absolute bioavailability of MK-0826 administered via the IM route.

**Multiple dose IM pharmacokinetics**

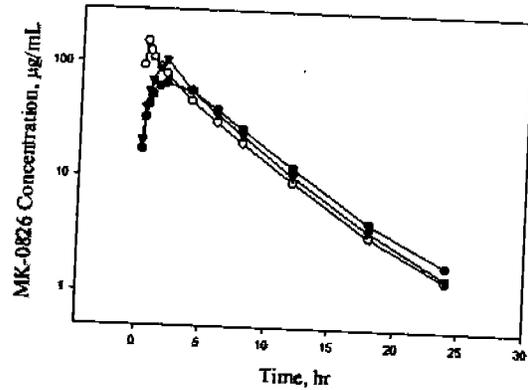
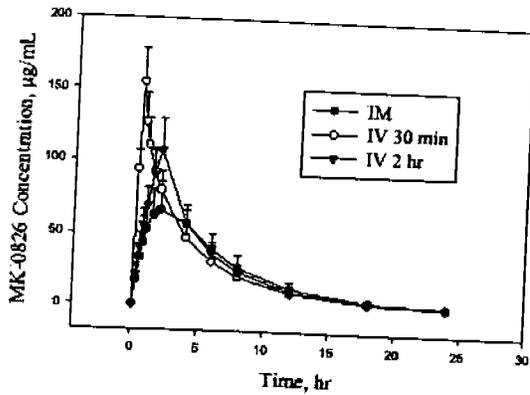
The sponsor performed a 2-part, randomized, placebo-controlled, single-dose, 3-period, crossover (Part A) and multiple-dose (Part B) study (P019) to investigate the pharmacokinetics, safety, and tolerability of the IM formulation of MK-0826 in 26 healthy subjects. In Part A, each subject received three single 1 g doses of MK-0826 (or placebo) administered IM, IV infused over 30 minutes, and IV infused over 2 hours. There was a washout interval of at least 7 days between each of the three doses in Part A. In Part B, fasted subjects received a 1 g IM dose of MK-0826 (or placebo) administered once daily for 7 days. The pharmacokinetic parameters comparing IM to IV administration are shown below.

Mean (SD) value for pharmacokinetic parameters based on total MK-0826 following 1 gram of MK-0826

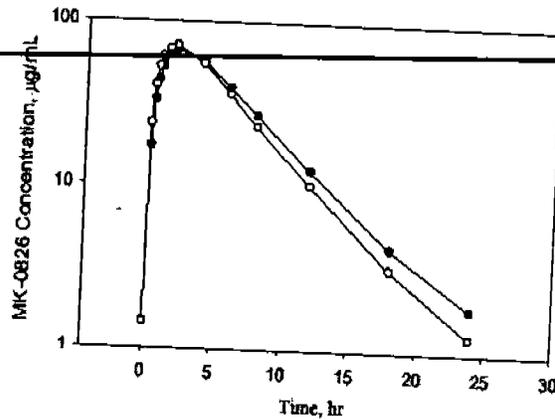
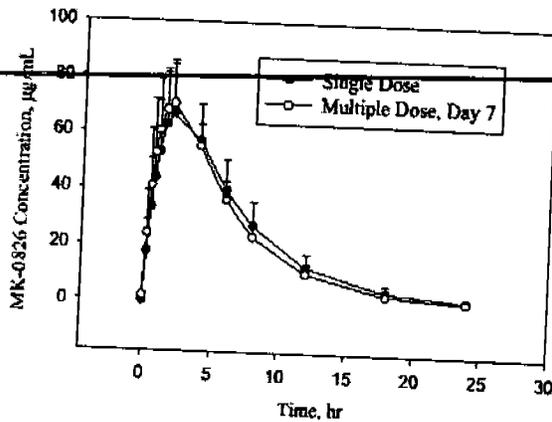
Parameter	1 g IM (Day 1) n=20	1 g IM (Day 7) n=18	1 g IV (30 min) n=19	1 g IV (2 hrs) n=19
$AUC_{0-24}$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	535.4 (102.7)	509.0 (78.0)	--	--
$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	546.8 (108.7)	--	608.2 (127.7)	600.2 (111.9)
$C_{eoi}$ ( $\mu\text{g}/\text{mL}$ )	--	--	164.6 (24.0)	120.8 (40.9)
$C_{max}$ ( $\mu\text{g}/\text{mL}$ )	72.2 (14.1)	75.7 (11.2)	--	--
$T_{max}$ (hrs)	2.3 (0.9)	1.9 (0.6)	--	--
Half-life (hrs)	3.84 (0.47)	3.52 (0.23)	3.82 (0.52)	3.72 (0.55)
$CL_T$ (mL/min)	--	--	28.4 (4.6)	28.6 (4.8)
$CL_R$ (mL/min)	11.1 (3.3)	13.7 (3.7)	12.7 (3.2)	11.9 (3.6)
$fe_{0-24}$ (% dose)	34.8 (9.0)	41.2 (10.0)	42.3 (10.1)	39.6 (11.9)

**APPEARS THIS WAY  
ON ORIGINAL**

The mean plasma concentration-time profiles of total MK-0826 from healthy subjects receiving a single dose of 1 g IM, 1 g IV over 30 minutes, and 1 g IV over 2 hours are shown below.



The mean plasma concentration-time profiles of total MK-0826 from healthy subjects on Day 1 following a single 1 g IM dose (Part 1) and on the seventh day following once-daily dosing for 7 days (Part 2) are shown below.



Similar to IV administration, no accumulation of MK-0826 was observed during IM administration from Day 1 to Day 7. The Day 7/Day 1 geometric mean ratio of the  $AUC_{0-24}$  was 0.9774. The lack of accumulation with multiple doses was similar to IV administration in which the rate of elimination increased following multiple doses compared to following a single dose.

#### Pharmacodynamics (IM vs. IV administration)

The sponsor calculated %T >MIC using an MIC of 4.0 µg/mL for total MK-0826 concentrations following 1 g IM and IV administration over 30 minutes. The reviewer also calculated the %T >MIC for unbound MK-0826 concentrations with an MIC of 4.0 and 1.0 (MIC equivalent to total MK-0826 concentration of approximately 15 µg/mL).

**%T >MIC following the administration of 1 gram IM on Day 1 and Day 7 as well as 1 gram IV**

Regimen	MIC (µg/mL)	%T >MIC	
		Total concentration	Unbound concentration*
1 g IM (Day 1)	4.0	76%	6%
1 g IM (Day 7)	4.0	72%	6%
1 g IV (0.5 hr infusion)	4.0	70%	12%
1 g IM (Day 1)	1.0	--	43%
1 g IM (Day 7)	1.0	--	41%
1 g IV (0.5 hr infusion)	1.0	--	38%

\* Estimated assuming unbound fraction is 0.06

The administration of 1 g MK-0826 IM or IV is estimated to provide a %T >MIC of at least 38% of the dosing interval using an MIC of 1.0 µg/mL. Based on in vivo animal studies, MK-0826 should demonstrate efficacy against most common pathogens with an MIC ≤1.0 µg/mL.

**Q. What is the absolute bioavailability following IM administration?**

The sponsor calculated the absolute bioavailability of 1 g MK-0826 administered IM during study P019. As part of this single-dose, 3-period, crossover study, the sponsor used 1 g MK-0826 IV administered over 120 minutes as the reference.

The geometric mean ratio of the AUC<sub>0-∞</sub> when administered IM compared to the AUC<sub>0-∞</sub> when administered IV over 30 min was 0.902. Thus, the absolute bioavailability of MK-0826 when administered IM is 90%.

Comparison	Parameter	Point Estimate	90% Confidence Interval
1 g IM (Day 1) vs. 1 g IV (30 min)	AUC <sub>0-∞</sub>	0.902	0.870 to 0.934

**Reviewers comments:**

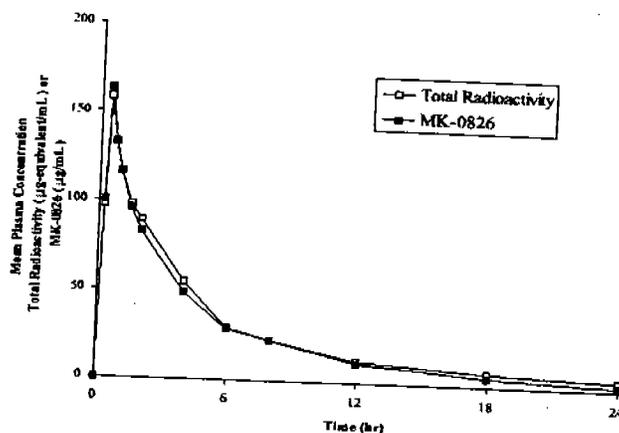
The sponsor estimated the absolute bioavailability of the IM formulation using the AUC<sub>0-∞</sub> of an IV dose infused over 2 hrs as the reference formulation in order to avoid any effect of nonlinear plasma protein binding. Although MK-0826 demonstrates concentration-dependent protein binding, the proposed administration is 1 g infused over 30 minutes. Thus, the reviewer calculated the absolute bioavailability of the IM formulation based on the AUC<sub>0-∞</sub> of 1 gram infused over 30 minutes and not over 2 hrs.

**Q. What is the metabolic fate of MK-0826 in humans?**

To investigate the metabolism of MK-0826 in humans, the sponsor conducted an open-label, single IV dose mass balance study (P012) of four male and three female subjects between the ages of 18 and 50. A single 1 g dose of <sup>14</sup>C-MK-0826 containing ~110 µCi of <sup>14</sup>C was infused over 30 minutes in the fasted state. Blood samples were collected for 48 hrs, urine samples for 168 hrs, and stool samples for 168 hrs to recovery the radioactivity. Plasma and urine samples were counted directly using liquid scintillation spectrometry. Fecal samples were homogenized, air-dried, combusted, and radioactivity of the resulting carbon dioxide determined using liquid scintillation spectrometry. Radioactivity profiles were determined by gradient elution liquid chromatography with in-line radiometric flow detection.

The mean plasma concentration-time profile of total MK-0826 (µg/mL) and total radioactivity (expressed as radioequivalents) following IV administration of <sup>14</sup>C-MK-0826 is shown in the figure below.

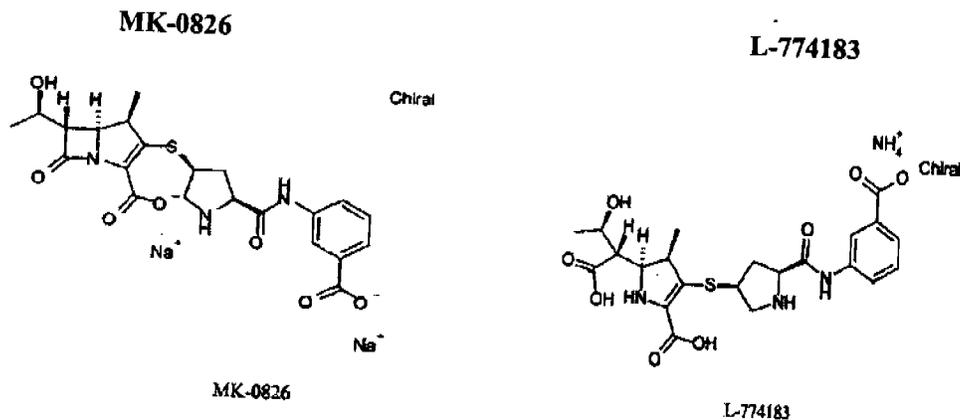
Mean plasma concentration-time profile of total MK-0826 and total radioactivity following IV administration of <sup>14</sup>C-MK-0826



The cumulative recovery of radioactivity up to 168 hrs was 89.7%. 80.5% of the total radioactivity was recovered from urine and 9.20% from feces.

Plasma AUC<sub>0-24</sub> values based on total radioactivity were similar to those based on unchanged MK-0826 in plasma (the ratio of unchanged MK-0826/total radioactivity ranged from  $\frac{1}{1}$  to  $\frac{1}{1}$ ). Thus, most of the drug in plasma was unchanged MK-0826.

Metabolic profiling of urine identified eight components accounting for radioactivity. MK-0826 and L-774183 (ring-opened metabolite) accounted for 37.5% and 36.7% of the administered dose recovered in urine, respectively. The remaining six metabolites accounting for 3.9% of the dose and were not identified. The structure of the major urinary metabolite (L-774183) is shown below.

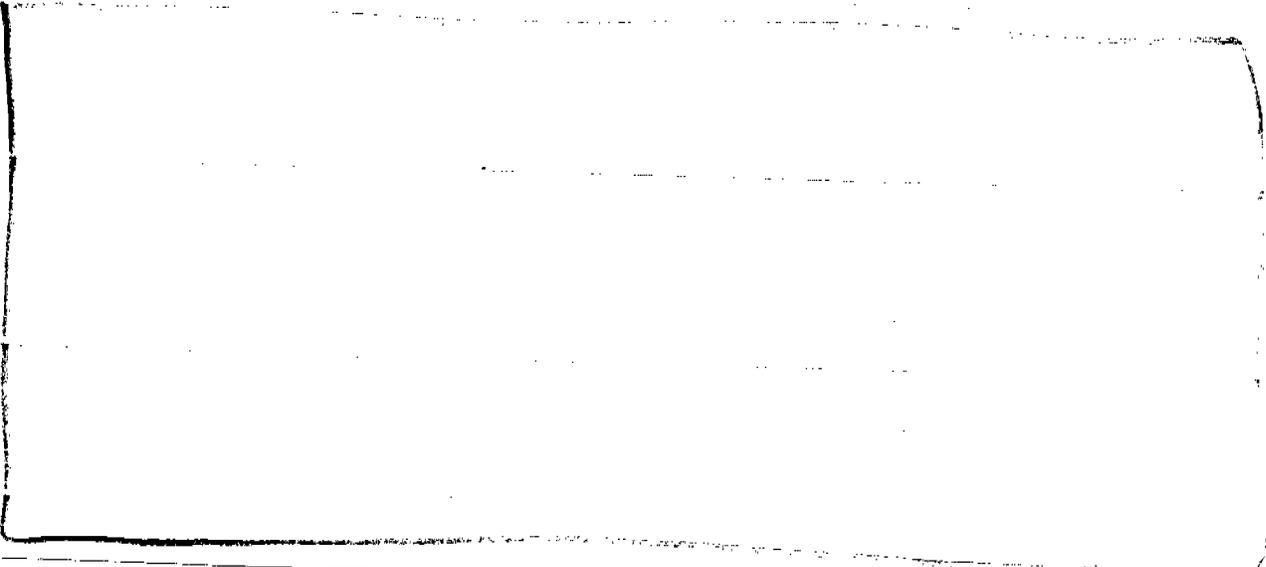


Differences in exposure based on unchanged MK-0826 concentration and total radioactivity were observed between male and female subjects (see table below). However, the small number of subjects, the greater age among female subjects (mean 47.7 yrs vs. 25.3 yrs) and racial and ethnic differences among male and female subjects (male: 1 Caucasian, 3 Black; female: 1 Caucasian, 1 Black, 1 Hispanic) may have contributed to differences seen between the two groups.

**Plasma AUC<sub>0-24</sub> total MK-0826 and total radioactivity following administration of 1 gram IV <sup>14</sup>C-MK-0826 in healthy subjects**

Subject	Gender	Total Radioactivity AUC <sub>0-24</sub> (µg eq*hr/mL)	Total MK-0826 AUC <sub>0-24</sub> (µg*hr/mL)	Ratio MK-0826/ Total radioactivity
1	M	655.8	615.0	0.94
2	M	618.0	635.4	1.03
3	M	612.2	580.3	0.95
4	M	484.3	463.7	0.96
5	F	707.5	633.1	0.89
6	F	711.7	657.6	0.92
7	F	733.3	641.7	0.88
Mean (SD)		646.1 (85.5)	603.8 (66.5)	0.94 (0.05)
90% CI		--	--	(0.90 to 0.97)

The sponsor also investigated the presence of active metabolites of MK-0826 in plasma and urine. In study P001, the total plasma and urine concentrations determined by \_\_\_\_\_ were compared to the concentration determined using a bioassay with *Bacillus subtilis* as the indicator organism. The plots comparing the sample concentrations from 1 \_\_\_\_\_ are shown below.



Plasma concentrations of total MK-0826 obtained by \_\_\_\_\_ demonstrated that \_\_\_\_\_ concentrations were similar or higher than concentrations obtained via bioassay, providing evidence for the lack of active metabolites. The plot of urine concentration from \_\_\_\_\_ vs. bioassay demonstrated that urine concentrations were slightly greater with bioassay. The deviation may be due to the small percentage of unidentified metabolites in the urine and are probably not clinically relevant.

**Q. What is the potential of MK-0826 to act as a substrate for and as an inhibitor of cytochrome P450 isoforms?**

To assess the metabolism of MK-0826 by human liver microsomes, 10 µM <sup>14</sup>C-MK-0826 was incubated with human liver microsomes at 37°C for 50 minutes. Control samples were prepared under the same conditions using boiled microsomes. No metabolic conversion of MK-0826 was detected over a 50-min incubation, suggesting that CYP isozymes are not involved in the metabolism of MK-0826.

The potential for MK-0826 to influence the metabolism of co-administered drugs was assessed in human liver microsomes using probe substrates for human CYP isozymes (1A2, 2C9, 2C19, 2D6, 2E1, and 3A4). At concentrations up to 500  $\mu\text{M}$  (240  $\mu\text{g/mL}$ ), MK-0826 did not inhibit the microsomal metabolism of probe substrates. Thus, plasma concentrations observed in patients receiving 1 g MK-0826 are unlikely to inhibit the clearance of drugs mediated by these CYP isozymes.

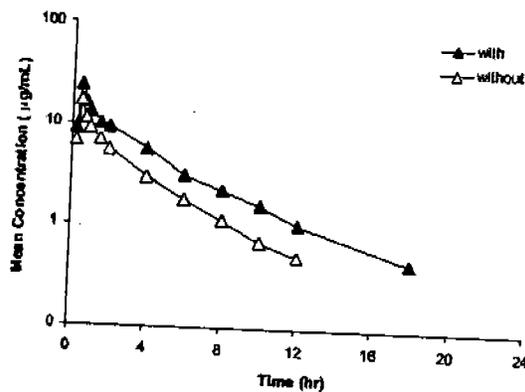
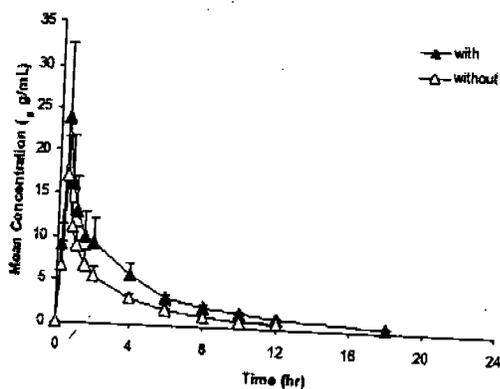
CYP P450 Isoform	Substrate	IC50 Value ( $\mu\text{M}$ )
1A2	Phenacetin	>500
2C9	Diclofenac	>500
3A4	Testosterone	>500

**Q. What is the potential of MK-0826 to act as a substrate for and an inhibitor of P-glycoprotein?**  
 To determine whether MK-0826 is a P-glycoprotein substrate/inhibitor, in vitro studies were performed using cell-based assay systems: transcellular transport studies with L-MDR1 (human MDR1 transfected porcine renal epithelial cells) and cellular accumulation studies with KB-V1 (human MDR1 P-gp overexpressing multi-drug resistant human epidermoid carcinoma cells). In both systems, MK-0826 showed no transport characteristics consistent with its being a P-glycoprotein substrate or inhibitor.

**Q. What is the effect of probenecid on the pharmacokinetics of MK-0826?**

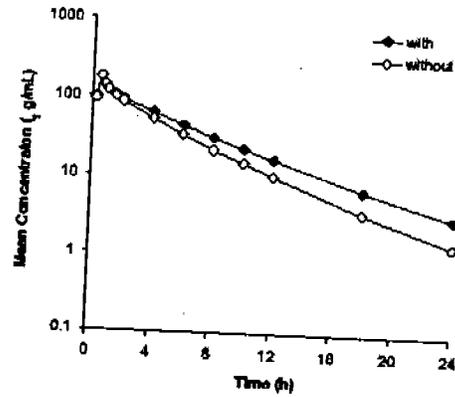
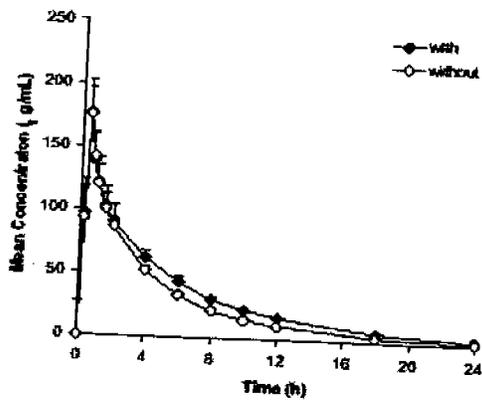
The sponsor investigated the interaction between probenecid and MK-0826 in a randomized, open-label, 2-period crossover study (P027) of 14 subjects assigned to receive oral probenecid 500 mg every 6 hrs for a total of 9 doses with a single 1 g IV dose of MK-0826 infused over 30 min or MK-0826 alone in a crossover fashion. Subjects were randomized to sequence groups stratified by gender. There were at least 7 days of washout between the MK-0826 doses in Periods 1 and 2.

Probenecid effectively prolonged plasma total and unbound MK-0826 concentrations. The mean plasma concentration-time profiles of unbound MK-0826 following a single 1 gram IV dose with and without probenecid are shown below.



The mean plasma concentration-time profiles of total MK-0826 following a single 1 gram IV dose with and without probenecid are shown in the figures below.

Mean plasma concentration-time profiles of total MK-0826 following a single 1 gram IV dose with and without probenecid



The arithmetic mean  $\pm$  SD pharmacokinetic parameters of unbound and total MK-0826 in subjects administered a single 1 g IV dose of MK-0826 with and without probenecid are shown below.

Parameter	Unbound MK-0826		Total MK-0826	
	MK-0826 alone	MK-0826 + Probenecid	MK-0826 alone	MK-0826 + Probenecid
<b>AUC<sub>0-24</sub> (<math>\mu\text{g}\cdot\text{hr}/\text{mL}</math>)</b>				
All	38.2 $\pm$ 6.1	66.7 $\pm$ 13.8	619.0 $\pm$ 62.5	769.6 $\pm$ 58.7
Males	34.7 $\pm$ 5.5	56.7 $\pm$ 7.6	589.6 $\pm$ 61.1	757.8 $\pm$ 67.8
Females	41.6 $\pm$ 4.7	76.7 $\pm$ 11.1	648.5 $\pm$ 51.9	781.4 $\pm$ 50.4
<b>C<sub>0</sub> (<math>\mu\text{g}/\text{mL}</math>)</b>				
All	16.9 $\pm$ 4.7	23.8 $\pm$ 8.7	175.3 $\pm$ 25.7	176.7 $\pm$ 30.7
Males	14.1 $\pm$ 3.5	17.1 $\pm$ 4.0	161.5 $\pm$ 26.3	156.9 $\pm$ 16.2
Females	19.7 $\pm$ 4.1	30.5 $\pm$ 6.5	189.2 $\pm$ 17.0	196.6 $\pm$ 29.3
<b>Plasma CL (<math>\text{mL}/\text{min}</math>)</b>				
All	447.0 $\pm$ 69.9	259.8 $\pm$ 52.3	27.2 $\pm$ 2.7	21.8 $\pm$ 1.7
Males	488.9 $\pm$ 66.8	298.4 $\pm$ 38.4	28.5 $\pm$ 2.7	22.1 $\pm$ 1.9
Females	405.1 $\pm$ 45.1	221.1 $\pm$ 30.9	25.8 $\pm$ 2.1	21.4 $\pm$ 1.4
<b>Renal CL (<math>\text{mL}/\text{min}</math>)</b>				
All	207 $\pm$ 36	98 $\pm$ 29	12.8 $\pm$ 2.3	8.5 $\pm$ 2.5
Males	208 $\pm$ 26	93 $\pm$ 25	11.7 $\pm$ 1.8	7.1 $\pm$ 1.8
Females	216 $\pm$ 44	102 $\pm$ 33	13.8 $\pm$ 2.4	9.9 $\pm$ 2.4
<b>Non-renal CL (<math>\text{mL}/\text{min}</math>)</b>				
All	241 $\pm$ 76	162 $\pm$ 56	14.4 $\pm$ 3.7	13.3 $\pm$ 3.0
Males	292 $\pm$ 72	205 $\pm$ 43	16.8 $\pm$ 3.3	15.1 $\pm$ 2.6
Females	189 $\pm$ 33	119 $\pm$ 25	12.0 $\pm$ 2.2	11.5 $\pm$ 2.4
<b>Half-life (hrs)*</b>				
All	3.3	4.3	4.0	4.8
Males	3.6	4.5	4.3	5.2
Females	3.0	4.2	3.8	4.5
<b>Fe<sub>0-24</sub> (fraction)</b>				
All	0.47 $\pm$ 0.10	0.38 $\pm$ 0.12	--	--
Males	0.41 $\pm$ 0.08	0.31 $\pm$ 0.08	--	--
Females	0.53 $\pm$ 0.07	0.45 $\pm$ 0.10	--	--

Fraction unbound (%)				
All	6.3 ± 0.5	8.7 ± 1.7	--	--
Males	6.0 ± 0.0	7.6 ± 1.0	--	--
Females	6.6 ± 0.5	9.9 ± 1.5	--	--

\* Harmonic mean

Probenecid statistically significantly reduced the unbound and total  $CL_T$  ( $p < 0.0001$ ), unbound and total  $CL_R$  ( $p < 0.0001$ ), urinary excretion of MK-0826 ( $p < 0.0001$ ), unbound  $CL_{NR}$  ( $p < 0.0001$ ), and total  $CL_{NR}$  ( $p = 0.0576$ ).

Probenecid also appeared to alter the protein binding of MK-0826 in plasma. The mean  $AUC_{0-\infty}$  unbound/total drug ratio increased from 6.1% to 8.7% ( $p < 0.0001$ ) following the administration of probenecid, representing a 40% increase in the unbound fraction of MK-0826. Similarly, the mean  $C_{coi}$  unbound drug/total drug ratio increased from 10% to 13% ( $p < 0.0001$ ) when administered with probenecid, representing a 38% increase in the unbound fraction. However, the contribution of probenecid altering the protein binding by displacement from albumin rather than increasing plasma concentrations of MK-0826 was not determined by the sponsor.

The point estimate and 90% confidence intervals for unbound and total MK-0826 are shown below for  $C_{coi}$ ,  $AUC_{0-\infty}$ ,  $CL_R$ , and  $CL_T$ .

Parameter	Unbound MK-0826	
	Point Estimate	90% Confidence Interval
$C_{coi}$ ( $\mu\text{g/mL}$ )	1.37	1.262 to 1.492
$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{hr/mL}$ )	1.73	1.652 to 1.820
Plasma clearance (mL/min)		
Renal clearance (mL/min)	0.46	0.434 to 0.495
	Total MK-0826	
$C_{coi}$ ( $\mu\text{g/mL}$ )	1.01	0.947 to 1.067
$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{hr/mL}$ )	1.25	1.195 to 1.299
Plasma clearance (mL/min)		
Renal clearance (mL/min)	0.65	0.601 to 0.700

Statistically significant gender differences were observed for  $CL_T$ ,  $CL_{NR}$ ,  $AUC_{0-\infty}$ , and  $C_{coi}$  for unbound MK-0826 and  $CL_R$ ,  $CL_{NR}$ ,  $fe$ , and  $C_{coi}$  for total MK-0826.

The pharmacokinetic differences between females and males may have been due to the greater unbound fraction of MK-0826 in females following administration of probenecid. Probenecid had a greater effect on protein binding in females than males and may have further increased the fraction unbound of MK-0826 in females compared to males.

#### Reviewers comments:

The dose of probenecid for the treatment of gout is 500 mg BID. Thus, the administration of probenecid 500 mg QID (recommended dose for elevation and prolongation of plasma levels with penicillins) may represent the greatest drug interaction that is likely to occur between probenecid and MK-0826.

#### Q. What is the effect of MK-0826 on the protein binding of warfarin in human plasma?

Using in vitro methods, maximal plasma concentrations of MK-0826 following the administration of 1 g IV (approximately 300  $\mu\text{M}$ ) resulted in an 8-9% increase in the unbound fraction of warfarin. The relative inability of MK-0826 to displace warfarin from albumin binding sites may provide evidence that

the two drugs bind to different sites on albumin. The clinical implication of concurrent administration of MK-0826 and warfarin may be a transient, small increase in the prothrombin time.

MK-0826 concentration (µM)	MK-0826 concentration (µg/mL)	Unbound fraction of warfarin (%)
0	0	2.54 ± 0.02
25	12	2.50 ± 0.09
50	24	2.56 ± 0.04
200	96	2.65 ± 0.05
300	144	2.77 ± 0.05
400	192	2.74 ± 0.14

**Q. What is the effect of renal function on the pharmacokinetics of MK-0826?**

The sponsor evaluated the effect of renal impairment on the pharmacokinetics of MK-0826 in an open-label, 2-period study (P015) to evaluate the pharmacokinetics, safety, and tolerability of MK-0826 in 24 subjects with varying degrees of renal function. In Period 1, 1 g of MK-0826 was administered as a single, 30 min IV infusion. The degree of renal impairment was defined as: mild (60 to 90 mL/min/1.73 m<sup>2</sup>), moderate (31 to 59 mL/min/1.73 m<sup>2</sup>), advanced (5 to 30 mL/min/1.73 m<sup>2</sup>), and end stage on hemodialysis (<10 mL/min/1.73 m<sup>2</sup>). For end-stage renal insufficiency patients, Period 1 was defined as a non-hemodialysis day. In Period 2, patients with end-stage renal insufficiency received a single 1-g dose of MK-0826 immediately prior to the initiation of hemodialysis (lasting 4 hrs). Periods 1 and 2 were separated by at least 10 days. Determination of creatinine clearance was based on the mean of 2 baseline 24-hour urine collections or the need for hemodialysis. The creatinine clearance of patients with end-stage renal disease on maintenance hemodialysis was assumed to be <10 mL/min/1.73 m<sup>2</sup>.

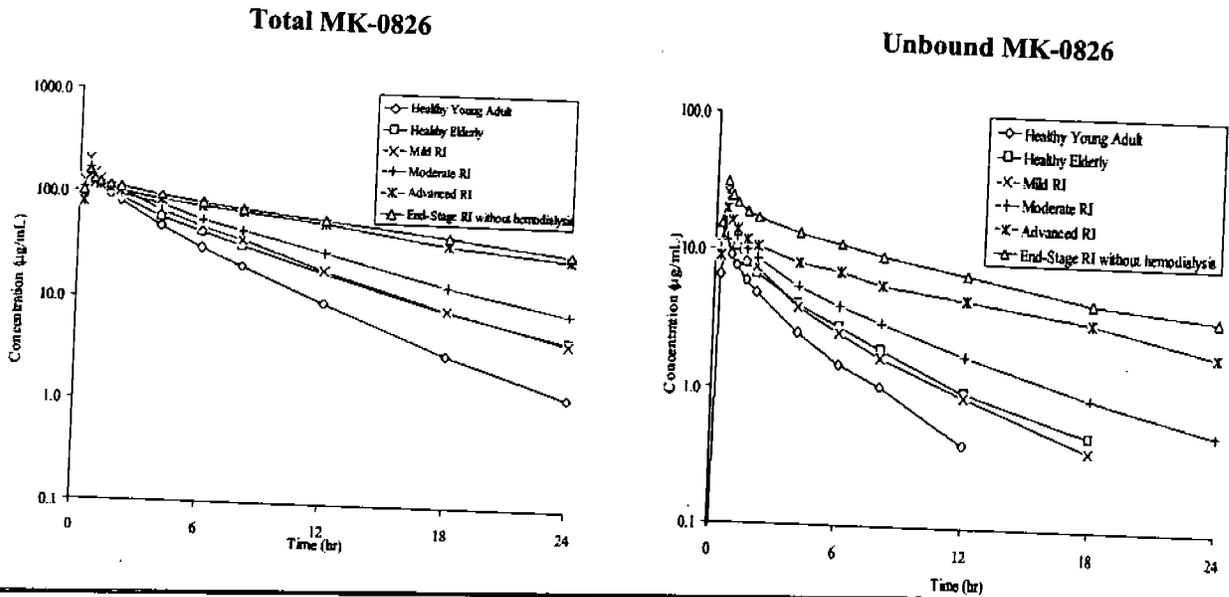
The mean (SD) demographics of the subjects by renal function group are shown below.

Renal function	N	Gender	Age (years)	Height (cm)	Weight (kg)	CL <sub>CR</sub> (mL/min)
Control*	16	8F/8M	32.8 (6.0)	172.8 (10.9)	69.6 (13.2)	112.6 (21.6)
Mild impairment	6	6F	68.8 (10.4)	159.3 (9.0)	68.8 (19.0)	77.5 (8.7)
Moderate impairment	7	3F/4M	53.0 (13.5)	173.0 (11.5)	82.9 (15.6)	45.3 (7.2)
Advanced impairment	6	3F/3M	52.5 (15.4)	169.2 (8.0)	86.0 (15.8)	19.8 (9.1)
End-stage impairment (w/o dialysis)	7	2F/5M	52.1 (14.3)	170.0 (7.8)	65.0 (13.6)	NC
End-stage impairment (w/ dialysis)	5	1F/4M	44.8 (13.3)	171.3 (4.2)	66.3 (12.3)	NC

\*Control subjects from study P009 (healthy young adults)

NC - urine samples not collected from patients with end-stage renal impairment

The mean plasma concentration-time profiles of total and unbound MK-0826 following a single 1 g IV dose in healthy young subjects (P009), healthy elderly subjects (P010), and patients with defined degrees of renal impairment are shown below.



The arithmetic mean (SD) pharmacokinetic parameters for total MK-0826 by renal function group following a single 1 gram IV dose are shown below.

Renal function	AUC <sub>0-∞</sub> (µg*hr/mL)	C <sub>eoi</sub> (µg/mL)	CL <sub>T</sub> (mL/min)	t <sub>1/2</sub> (hrs)	CL <sub>R</sub> (mL/min)	CL <sub>NR</sub> (mL/min)	Fe <sub>0-36</sub> (%)
<b>Total MK-0826</b>							
Control*	572 (69)	154.9 (22.0)	29.5 (3.4)	3.9 (0.5)	12.7 (4.2)	16.8 (5.6)	43.1 <sup>a</sup> (14.7)
Mild impairment	800 (194)	181.7 (25.7)	21.8 (5.1)	5.0 (1.2)	8.5 (1.5)	13.3 (3.8)	39.8 (5.3)
Moderate impairment	1036 (229)	166.2 (26.6)	17.0 (4.9)	6.9 (1.5)	6.5 (2.0)	10.5 (3.3)	38.3 (7.4)
Advanced impairment	1747 (414)	124.8 (17.3)	10.0 (2.5)	12.9 (2.1)	2.3 (1.1)	7.7 (1.9)	22.5 (9.3)
End-stage impairment (w/o dialysis)	2038 (764)	148.0 (14.3)	9.2 (3.2)	12.9 (4.3)	NC	NC	NC
End-stage impairment (w/ dialysis)	1622 (654)	120.4 (30.7)	11.6 (4.2)	17.4 (5.8)	NC	NC	NC

\*Control subjects from P009.

a - Fe<sub>0-24</sub>

NC - urine samples not collected from patients with end-stage renal impairment

The arithmetic mean (SD) pharmacokinetic parameters for unbound MK-0826 by renal function group following a single 1 gram IV dose are shown below.

Renal function	AUC <sub>0-∞</sub> (μg*hr/mL)	C <sub>eoI</sub> (μg/mL)	CL <sub>T</sub> (mL/min)	t <sub>1/2</sub> (hrs)	CL <sub>R</sub> (mL/min)	CL <sub>NR</sub> (mL/min)	Fe <sub>0-36</sub> (%)
<b>Unbound MK-0826</b>							
Control*	33.2 (5.5)	12.9 (3.2)	513.6 (80.3)	--	217.2 (67.8)	296.5 (112.7)	43.1 <sup>a</sup> (14.7)
Mild impairment	51.9 (15.2)	23.4 (7.8)	338.7 (71.3)	4.7 (1.3)	130.3 (23.4)	208.4 (53.0)	39.8 (5.3)
Moderate impairment	78.9 (22.6)	21.4 (5.6)	233.4 (92.5)	6.1 (1.6)	86.0 (32.6)	147.4 (63.0)	38.3 (7.4)
Advanced impairment	145.8 (32.4)	17.7 (1.8)	119.2 (26.4)	10.4 (1.0)	25.8 (13.7)	93.3 (18.9)	22.5 (9.3)
End-stage impairment (w/o dialysis)	253.3 (48.5)	28.5 (9.3)	68.4 (16.3)	11.6 (3.3)	NC	NC	NC
End-stage impairment (w/ dialysis)	160.9 (38.0)	28.3 (8.1)	108.3 (25.4)	16.4 (3.0)	NC	NC	NC

\*Control subjects from P009

a - Fe<sub>0-24</sub>

NC - urine samples not collected from patients with end-stage renal impairment

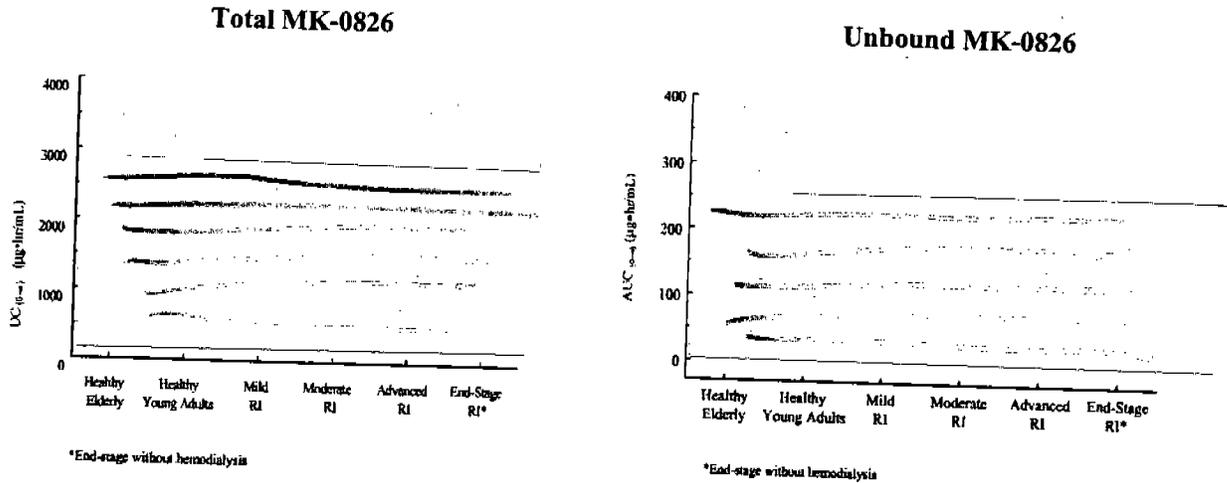
The total MK-0826 C<sub>eoI</sub> increased with mild and moderate renal impairment only, whereas C<sub>eoI</sub> increased more than two-fold for unbound MK-0826 concentrations as renal impairment increased. The half-life was prolonged with decreasing creatinine clearance for both total and unbound MK-0826 concentrations.

The MK-0826 AUC<sub>0-∞</sub> increased as creatinine clearance decreased for total and unbound concentrations. The increase in unbound AUC<sub>0-∞</sub> was greater than total AUC<sub>0-∞</sub> for a corresponding creatinine clearance.

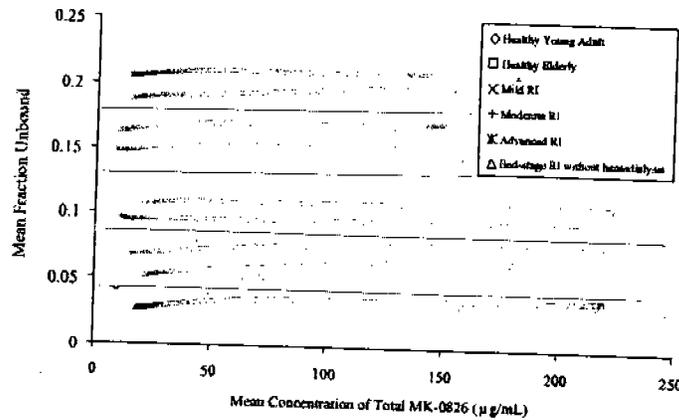
The increase in unbound AUC<sub>0-∞</sub> was greater than total AUC<sub>0-∞</sub> for a corresponding creatinine clearance. Individual values and geometric means with 90% confidence intervals for total and unbound MK-0826 AUC<sub>0-∞</sub> following a 1 gram IV dose of MK-0826 for healthy adult subjects (study 009), healthy elderly subjects (study 010), and subjects with varying degrees of renal insufficiency are shown below.

**APPEARS THIS WAY  
ON ORIGINAL**

Relationship between total and unbound MK-0826  $AUC_{0-\infty}$  in healthy young subjects (P009), healthy elderly subjects (P010), and subjects with varying degrees of renal impairment (individual values [○] and geometric mean values [●] with 90% confidence intervals)



The fraction of unbound MK-0826 also increased as the severity of renal impairment increased. The fraction of unbound MK-0826 in healthy elderly subjects was similar to subjects with mild renal impairment.



The mean pharmacokinetic parameter ratios (control subjects/renal impairment subjects) are shown below. The  $AUC_{0-\infty}$  increased more for unbound than total MK-0826 with increasing renal impairment, whereas  $CL_T$ ,  $CL_R$ , and  $CL_{NR}$  decreased more for unbound than total MK-0826 with increasing renal impairment.

Although the renal clearance declined more than 5-fold for total drug and 8-fold for unbound drug between control subjects and subjects with advanced impairment, the fraction of MK-0826 excreted unchanged in the urine only decreased approximately two-fold with declining creatinine clearance.

**Geometric mean ratios (renal impairment/control) and 90% CIs for pharmacokinetic parameters using total MK-0826 concentrations**

Parameter		Mild	Moderate	Advanced	End-stage (w/o dialysis)	End-stage (w/ dialysis)
AUC <sub>0-∞</sub> (µg*hr/mL)	Ratio	1.37	1.78	3.00	3.38	2.68
	90% CI	(1.14 - 1.66)	(1.49 - 2.12)	(2.49 - 3.62)	(2.83 - 4.03)	
C <sub>coi</sub> (µg/mL)	Ratio	1.17	1.18	0.91	0.93	0.79
	90% CI	(1.08 - 1.26)	(1.09 - 1.27)	(0.84 - 0.98)	(0.87 - 1.00)	
CL <sub>T</sub> (mL/min)	Ratio	0.73	0.56	0.33	0.30	0.37
	90% CI	(0.60 - 0.88)	(0.47 - 0.67)	(0.28 - 0.40)	(0.25 - 0.35)	
t <sub>1/2</sub> (hrs)*	Ratio	1.23	1.73	3.32	3.12	4.16
	90% CI	--	--	--	--	
CL <sub>R</sub> (mL/min)	Ratio	0.70	0.52	0.16	NC	NC
	90% CI	(0.51 - 0.97)	(0.38 - 0.71)	(0.12 - 0.23)		
CL <sub>NR</sub> (mL/min)	Ratio	0.81	0.68	0.49	NC	NC
	90% CI	(0.61 - 1.06)	(0.52 - 0.88)	(0.38 - 0.64)		
F <sub>e0-36</sub> (% dose)	Ratio	0.93	0.90	0.48	NC	NC
	90% CI	(0.67 - 1.30)	(0.66 - 1.22)	(0.35 - 0.65)		

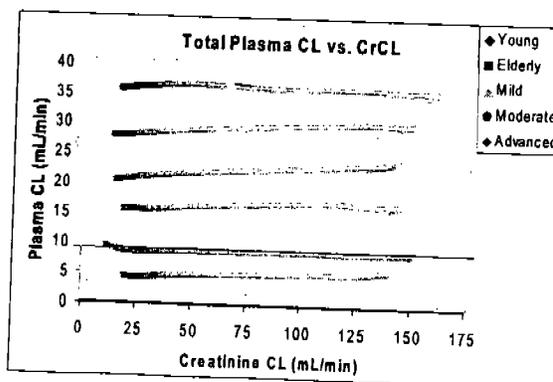
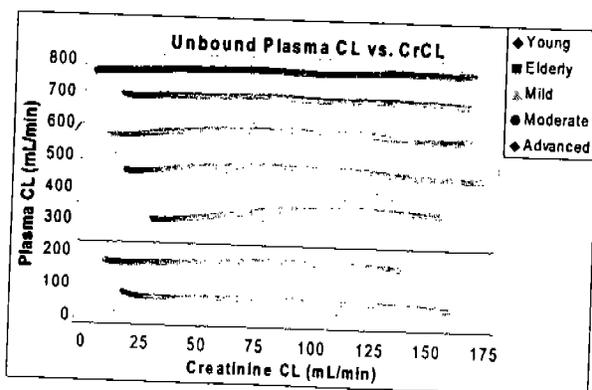
NC - Urine samples not collected from patients with end-stage renal impairment  
\* Harmonic mean

**Geometric mean ratios (renal impairment/control) and 90% CIs for pharmacokinetic parameters using unbound MK-0826 concentrations**

Parameter		Mild	Moderate	Advanced	End-stage (w/o dialysis)	End-stage (w/ dialysis)
AUC <sub>0-∞</sub> (µg*hr/mL)	Ratio	1.53	2.30	4.35	7.58	4.79
	90% CI	(1.28 - 1.84)	(1.93 - 2.74)	(3.62 - 5.23)	(6.36 - 9.02)	
C <sub>coi</sub> (µg/mL)	Ratio	1.76	1.96	1.75	2.04	2.29
	90% CI	(1.49 - 2.07)	(1.66 - 2.31)	(1.46 - 2.09)	(1.74 - 2.39)	
CL <sub>T</sub> (mL/min)	Ratio	0.65	0.43	0.23	0.13	0.21
	90% CI	(0.54 - 0.78)	(0.37 - 0.52)	(0.19 - 0.28)	(0.11 - 0.16)	
CL <sub>R</sub> (mL/min)	Ratio	0.62	0.39	0.11	NC	NC
	90% CI	(0.45 - 0.86)	(0.29 - 0.54)	(0.08 - 0.15)		
CL <sub>NR</sub> (mL/min)	Ratio	0.71	0.53	0.34	NC	NC
	90% CI	(0.52 - 0.97)	(0.39 - 0.71)	(0.25 - 0.46)		

NC - urine samples not collected from patients with end-stage renal impairment

The plasma clearances based on unbound and total MK-0826 were associated with CL<sub>CR</sub> as shown in the plots below ( $r^2=0.7207$  and  $r^2=0.7206$ , respectively). Consequently, the unbound and total AUC<sub>0-∞</sub> were also strongly associated with CL<sub>CR</sub> ( $r^2=0.6730$  and  $r^2=0.6557$ , respectively).



The plasma clearance of total MK-0826 was increased by approximately 30% when hemodialysis (4 hr session) was performed immediately following drug administration (within 5 minutes to 39 minutes following the end of infusion). The plasma clearance of unbound MK-0826 was increased by approximately 67%. About one-third of an administered dose of MK-0826 was recovered in the dialysate fluid after a four hour dialysis session.

Dosage adjustments of MK-0826 are necessary in patients with renal impairment to prevent an increased incidence of adverse events as well as maintain similar pharmacodynamics compared to patients with normal renal function.

**Justification of dosage adjustment**

The dose of MK-0826 used in phase 3 clinical studies was 1 g q24h for subjects with creatinine clearance >30 mL/min/1.73 m<sup>2</sup> and 500 mg q24h for subjects with creatinine clearance ≤30 mL/min/1.73 m<sup>2</sup> and not receiving hemodialysis.

Safety: The incidence of adverse events from phase 2b and phase 3 studies were compared between patients with creatinine clearance ≥60 mL/min/1.73 m<sup>2</sup> (N=1389, N=687, and N=537 for MK-0826, piperacillin/tazobactam, and ceftriaxone, respectively) and those with creatinine clearance ≤60 mL/min/1.73 m<sup>2</sup> (N=357, N=87, and N=213 for MK-0826, piperacillin/tazobactam, and ceftriaxone, respectively). In clinical studies, MK-0826 1 g IV once daily was administered to patients with creatinine clearance >30 mL/min/1.73 m<sup>2</sup>. The incidence of adverse events of MK-0826 were compared to piperacillin/tazobactam and ceftriaxone. ~~In general, the incidence of adverse events increased for all three antimicrobials in patients with creatinine clearance ≤60 mL/min/1.73 m<sup>2</sup>, although the occurrence of adverse events increased in a similar fashion for all three antimicrobials in subjects with renal impairment.~~

Pharmacodynamics: The %T >MIC based on total and unbound MK-0826 concentrations were calculated for each subject using the sponsor's proposed dosages for normal renal function (study P009) and mild, moderate, advanced, and end stage renal impairment (study P015). Based on the %T >MIC (unbound fraction) in subjects with normal renal function, a decrease in the dosage to 0.5 grams once daily is justified for patients with creatinine clearance >30 mL/min/1.73 m<sup>2</sup>, as well as a further decrease in the dosage to 0.25 grams once daily in patients with end stage renal function (creatinine clearance <10 mL/min/1.73 m<sup>2</sup>). The %T >MIC for total and unbound MK-0826 concentrations are shown in the table below.

**Median (range) %T >MIC\* based on simulated total and unbound MK-0826 concentrations for subjects with varying degrees of renal impairment**

Renal function	Total concentration			Unbound concentration		
	1 gram qd	0.5 grams qd	0.25 grams qd	1 gram qd	0.5 grams qd	0.25 grams qd
Normal	25%	---	---	21%	---	---
Mild	39%	---	---	33%	---	---
Moderate	51%	25%	---	57%	32%	---
Advanced	---	58%	---	---	88%	---
End-Stage	---	66%	13%	---	100%	61%

\*MIC = 32 µg/mL for total concentrations, MIC = 2 µg/mL for unbound concentrations

The reviewer agrees with the sponsor's dosing recommendations that the 1 g dose of MK-0826 does not need to be reduced in patients with renal impairment until the creatinine clearance is 30 mL/min/1.73 m<sup>2</sup> based on safety data and pharmacodynamics. In addition, 0.5 grams once daily is recommended for

patients with creatinine clearance  $\leq 30$  mL/min/1.73 m<sup>2</sup> since this was the dose used in phase 3 clinical studies and the available safety data.

**Recommended dosage of MK-0826 based on renal function**

Renal function	Recommended dose
Mild impairment (60 to 90 mL/min/1.73 m <sup>2</sup> )	1 gram q24h
Moderate impairment (31 to 59 mL/min/1.73 m <sup>2</sup> )	1 gram q24h
Advanced impairment (5 to 30 mL/min/1.73 m <sup>2</sup> )	0.5 grams q24h
End-stage (w/o dialysis) ( $<10$ mL/min)	0.5 grams q24h
End-stage (w/ dialysis) ( $<10$ mL/min/1.73 m <sup>2</sup> )	0.5 grams q24h 150 mg supplementary dose (30%)*

\*If MK-0826 is given within 6 hrs prior to hemodialysis

**Reviewers comments:**

The renal impairment study consisted of a single-dose pharmacokinetic study in subjects with varying degrees of renal impairment. The sponsor did not enroll healthy volunteers as a control group. Thus, study P009 (healthy young subjects) and study P010 (healthy elderly subjects) were used as historical controls. The sponsor stated that the two populations were combined since the mean age closely resembled the aggregate of patients with renal impairment. Due to differences in the pharmacokinetic parameters between healthy young and healthy elderly subjects, only study P009 was used in comparisons with subjects with renal impairment. Thus, all ratios comparing renal impairment to control subjects utilized only study P009.

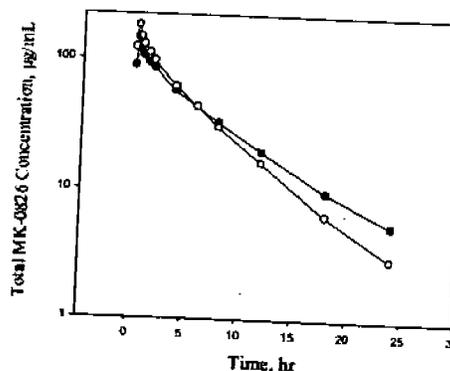
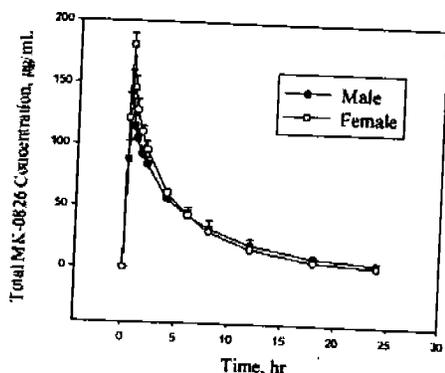
The reviewers' proposed dosage reduction is based on available safety data as well as pharmacokinetics and pharmacodynamics of unbound MK-0826. Unbound pharmacokinetic parameters were utilized since the pharmacological effect is dependent upon the unbound drug concentration. The sponsor stated that their dose reductions in renal impairment were based solely on total drug AUC<sub>0-∞</sub> since dose reductions based on unbound drug AUC<sub>0-∞</sub> would be expected to be much more substantial and may potentially result in suboptimal efficacy. This fails to take into consideration differences with the fraction unbound in renal impairment.

**Q. What is the effect of age on the pharmacokinetics of MK-0826?**

To determine the effect of age, the sponsor performed an open-label, 2-period, fixed-sequence study (P010) in 14 healthy elderly subjects 65 yrs of age or older (7 males and 7 females). Each subject received MK-0826 1 g IV once daily for 7 days in Period 1 and a single IV dose of 2 g in Period 2. Both the 1 g and 2 g doses were infused over 30 minutes. There was at least a 7-day washout interval between the 2 periods.

The mean plasma concentration-time profiles following the administration of 1 g MK-0826 IV (Day 1) in elderly men and women are shown below.

**Mean plasma concentration-time profiles following the administration of 1 g MK-0826 IV (Day 1) in elderly men and women**



**Arithmetic mean (SD) pharmacokinetic parameters of total MK-0826 in healthy elderly subjects**

Dose (g)	AUC* (µg*hr/mL)	C <sub>coi</sub> (µg/mL)	CL <sub>T</sub> (mL/min)	CL <sub>T</sub> (mL/min/kg)	CL <sub>R</sub> (mL/min)	Half-life (hrs)	Fe <sub>0-24</sub> (%)
Day 1 - 1g	782 (96)	160 (22)	21.6 (2.6)	0.30 (0.05)	8.6 (2.2)	5.3 (0.8)	37.6 (9.5)
Day 7 - 1g	682 (60)	155 (19)	24.6 (2.2)	0.34 (0.06)	9.7 (2.7)	5.1 (0.8)	39.6 (11.4)
2g	1226 (118)	278 (34)	27.4 (2.5)	0.38 (0.06)	10.4 (3.1)	5.1 (0.8)	36.5 (10.1)
Male/Day 1 - 1g	788 (123)	145 (15)	21.6 (3.3)	0.27 (0.04)	8.0 (2.8)	5.8 (0.7)	34.0 (11.4)
Male/Day 7 - 1g	691 (72)	142 (7)	24.3 (2.6)	0.31 (0.03)	8.5 (2.9)	5.6 (0.6)	35.2 (12.4)
Male/2g	1249 (146)	254 (7)	27.0 (3.1)	0.34 (0.03)	9.1 (3.0)	5.6 (0.7)	32.1 (9.9)
Female/Day 1 - 1g	773 (52)	180 (10)	21.6 (1.4)	0.34 (0.04)	9.4 (0.7)	4.6 (0.4)	42.5 (2.5)
Female/Day 7 - 1g	669 (42)	172 (17)	25.0 (1.6)	0.39 (0.05)	11.3 (1.2)	4.3 (0.2)	45.4 (6.9)
Female/2g	1195 (66)	310 (27)	28.0 (1.6)	0.44 (0.04)	12.1 (2.4)	4.5 (0.4)	42.4 (7.2)

\*AUC<sub>0-∞</sub> used for Day 1 - 1 g & 2 g; AUC<sub>0-24</sub> used for Day 7 - 1 g

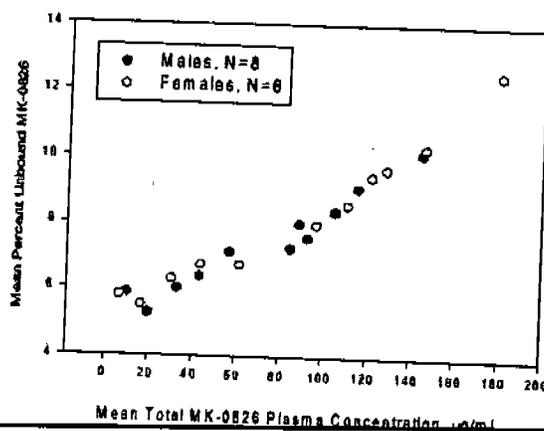
**Arithmetic mean (SD) pharmacokinetic parameters of unbound MK-0826 in healthy elderly subjects**

Dose (g)	AUC* (µg*hr/mL)	C <sub>coi</sub> (µg/mL)	CL <sub>T</sub> (mL/min)	CL <sub>T</sub> (mL/min/kg)	CL <sub>R</sub> (mL/min)	Half-life (hrs)
Day 1 - 1g	55.4 (7.6)	18.1 (4.6)	307 (44)	4.3 (0.7)	122 (29)	4.9 (1.1)
Day 7 - 1g	47.5 (7.0)	16.5 (3.6)	358 (49)	5.0 (0.9)	140 (37)	4.8 (0.8)
2g	121.2 (15.4)	57.8 (18.0)	279 (36)	3.9 (0.3)	103 (27)	5.2 (0.9)
Male/Day 1 - 1g	53.3 (8.2)	14.8 (2.7)	319 (49)	4.0 (0.6)	118 (36)	5.6 (1.0)
Male/Day 7 - 1g	47.5 (7.8)	14.2 (1.9)	359 (55)	4.5 (0.5)	124 (40)	5.3 (0.5)
Male/2g	111.9 (11.5)	45.6 (2.5)	301 (31)	3.8 (0.4)	99 (33)	5.7 (0.7)
Female/Day 1 - 1g	58.1 (6.3)	22.6 (2.2)	290 (32)	4.6 (0.7)	128 (15)	4.1 (0.4)
Female/Day 7 - 1g	47.4 (6.5)	19.5 (3.2)	357 (44)	5.6 (1.0)	160 (22)	4.1 (0.5)
Female/2g	133.5 (10.5)	74.1 (16.6)	251 (19)	3.9 (0.3)	107 (17)	4.5 (0.6)

\*AUC<sub>0-∞</sub> used for Day 1 - 1 g & 2 g; AUC<sub>0-24</sub> used for Day 7 - 1 g

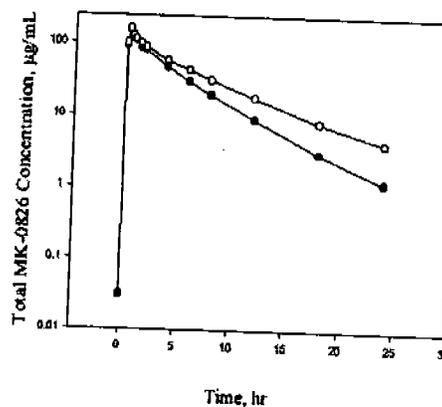
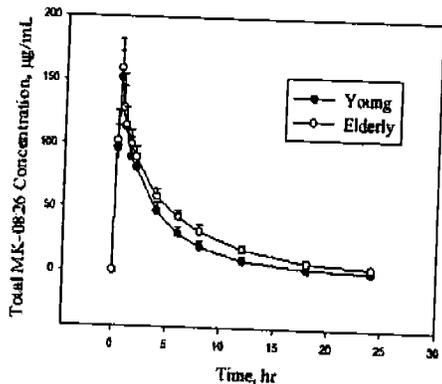
There were no statistically significant differences in the unbound and total  $AUC_{0-\infty}$  between male and female subjects. However, the unbound  $C_{\infty}$  was statistically significantly greater in elderly females than males ( $p=0.0006$ ) and the terminal half-life was statistically significantly shorter in elderly females than males ( $p=0.0010$ ).

The difference in pharmacokinetics between elderly males and females did not appear to be the result of differences in protein binding, as the fraction unbound of MK-0826 following administration of a 1 g dose was similar between healthy elderly males and females.



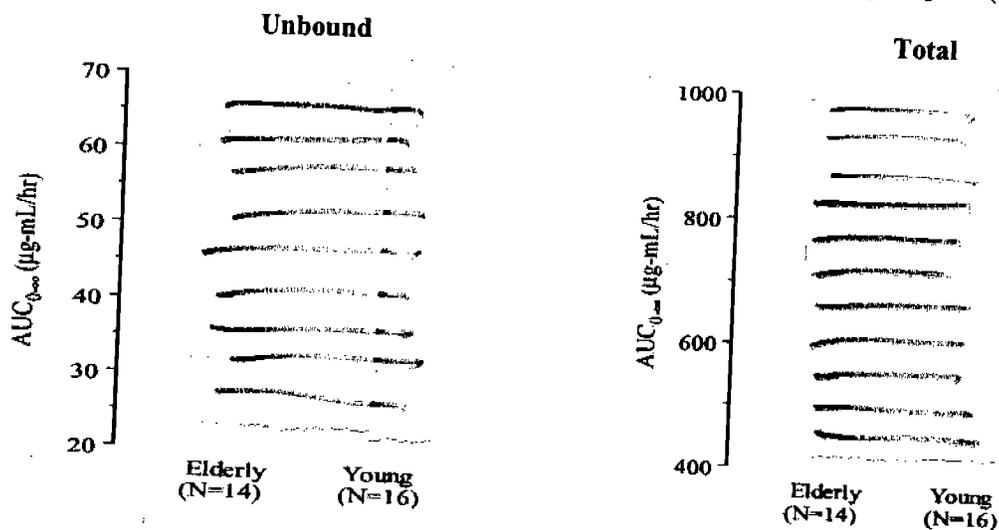
When compared to young subjects, healthy elderly subjects had greater plasma concentrations and a longer terminal half-life as shown in the figures below.

Mean (SD) plasma concentration of total MK-0826 following administration of a single 1 g dose in elderly (n=14) and data from young adults (n=16, study P009)



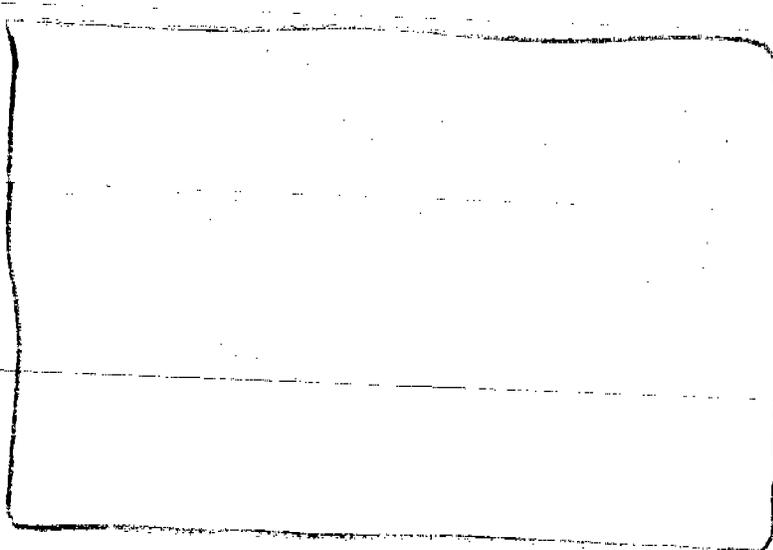
The  $AUC_{0-\infty}$  of unbound and total MK-0826 following the administration of 1 and 2 g doses were statistically significantly greater in elderly subjects than young subjects ( $p<0.0001$ ). Compared to young subjects, the mean  $AUC_{0-\infty}$  of unbound MK-0826 was 67% and 58% greater for 1 g and 2 g doses, respectively and the mean  $AUC_{0-\infty}$  of total MK-0826 was 37% and 21% greater for 1 g and 2 g doses, respectively in elderly subjects.

Individual (○, □) and geometric mean (●, ■)  $AUC_{0-\infty}$  values for unbound and total MK-0826 following a single 1 g IV dose in healthy elderly subjects and healthy young subjects (study P009)

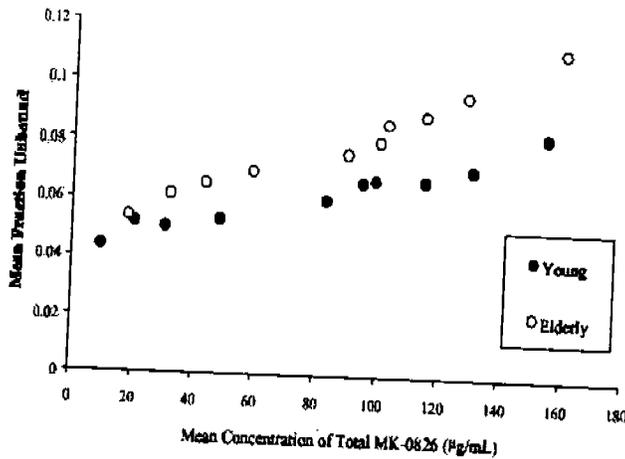


Renal clearance was statistically significantly decreased in elderly subjects compared to young adults ( $p \leq 0.0040$ ). Compared to young adults, renal clearance in elderly subjects was only 56% and 53% based on unbound drug for 1 g and 2 g doses, respectively, and 68% and 70% based on total drug for the 1 g and 2 g doses, respectively. Despite the decrease in  $CL_R$ , the  $F_e$  only decreased from 43.1% in young subjects to 37.6% in elderly subjects.

Differences in  $CL_T$  were observed between healthy young and healthy elderly subjects. These differences were related to  $CL_{CR}$  and may explain some of the variability in  $AUC_{0-\infty}$  between the two groups ( $r^2 = 0.4974$ ).

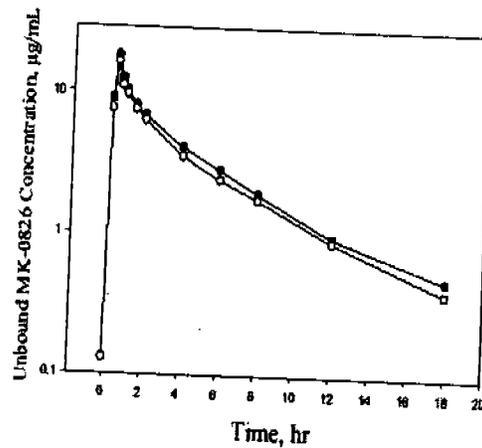
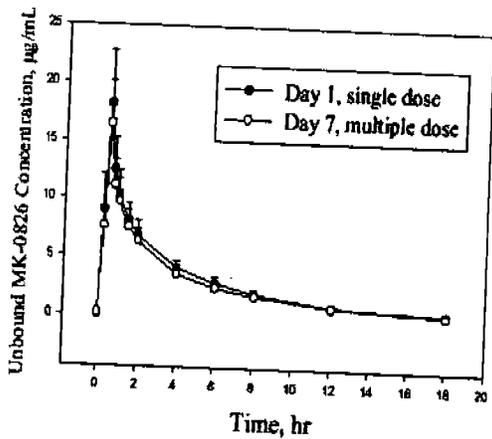


In addition, the unbound fraction of MK-0826 was greater in elderly subjects following the administration of 1 g IV compared to young adults. The difference was dependent on the MK-0826 concentration. Thus, elderly subjects will be exposed to unbound MK-0826 concentrations similar to subjects with mild renal impairment.



Following the administration of 1 g once daily for 7 days in healthy elderly subjects, the plasma concentration-time profile of total MK-0826 were similar between Day 1 and Day 7.

Mean (SD) plasma concentration profiles for unbound MK-0826 on Day 1 and Day 7 following a 1 g once-daily IV dose for 7 days in elderly subjects (n=14)



There was no accumulation following once-daily administration of 1 g MK-0826 IV for 7 days as shown with healthy elderly subjects. However, the Day 7  $AUC_{0-24}$  was statistically significantly less than the Day 1  $AUC_{0-24}$  based on unbound (GMR = 0.86,  $p < 0.0001$ ) and total MK-0826 concentrations (GMR = 0.88,  $p < 0.0001$ ).

**Reviewer comments:**

The sponsor was unable to explain the finding that plasma concentrations after multiple dosing were less than after a single dose. Similar findings were found in healthy young subjects only after multiple dose administration of 3 g IV MK-0826.

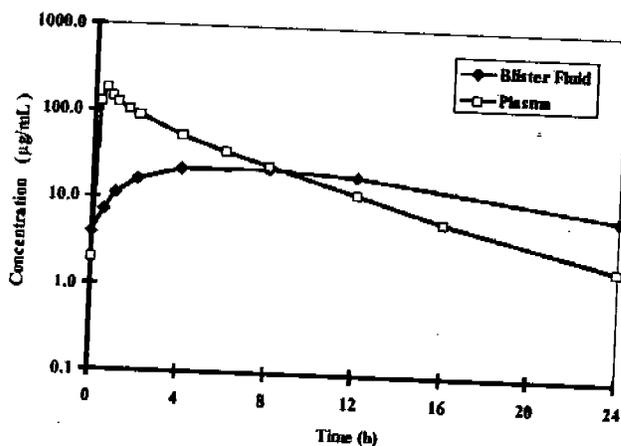
Differences in unbound and total  $AUC_{0-\infty}$  and  $CL_T$  between elderly subjects and young subjects are related to reduced creatinine clearance and decreased protein binding. Dosing adjustments in elderly patients are not necessary unless an adjustment is warranted based on reduced renal function.

**Q. Does MK-0826 distribute to tissues?**

The sponsor performed an open-label, multiple-dose study (P026) in 12 subjects to investigate the penetration of MK-0826 into suction-induced skin blisters on the third day of 1 g once-daily IV dosing. Skin blisters were formed 12 hours prior to drug administration on Day 3 and each blister sampled only once in conjunction with corresponding plasma samples.

The mean concentration profiles of total MK-0826 in plasma and skin blister fluid on the third day following the administration of 1 g MK-0826 once daily are shown below.

**Mean concentration-time profiles of total MK-0826 in plasma and skin blister fluid on the third day following the administration of 1 g MK-0826 daily**



The maximum concentration of MK-0826 in blister fluid occurred at about 8 hrs post-dose. Skin blister fluid concentrations declined more slowly than plasma concentrations, resulting in greater MK-0826 concentrations in blister fluid compared to plasma at the 12 and 24 hr samples.

The pharmacokinetic parameters of MK-0826 in plasma and blister fluid on Day 3 are shown below.

**Pharmacokinetic parameters of MK-0826 in plasma and blister fluid on the third day following administration of 1 g MK-0826 once daily**

Parameter	Plasma	Skin blister fluid
<b>C<sub>max</sub> or C<sub>tot</sub> (µg/mL)</b>		
Mean (SD)	N=12	N=12
Geometric mean	193.9 (30.3)	25.4 (4.4)
GMR (90% CI)	191.9	25.0
<b>C<sub>24</sub> (µg/mL)*</b>		0.13 (0.12 to 0.15)
Mean (SD)	N=10	N=12
Geometric mean	2.1 (0.8)	7.8 (1.8)
GMR (90% CI)	1.9	7.6
<b>AUC<sub>0-24</sub> (µg*hr/mL)</b>		3.96 (3.20 to 4.76)
Mean (SD)	N=12	N=12
Geometric mean	694.4 (100.5)	422.2 (66.0)
GMR (90% CI)	688.1	417.5
		0.61 (0.56 to 0.65)

\*Concentration at 24 hrs post-dose

The skin blister fluid AUC<sub>0-24</sub> /plasma AUC<sub>0-24</sub> geometric mean ratio was 0.61 and the 90% confidence interval ranged from           

The concentration of total MK-0826 in skin blister fluid remained above 4.0 µg/mL (estimated MIC<sub>90</sub>) throughout the entire dosing interval. However, protein binding of Mk-0826 in skin blister fluid was not determined.

**Reviewers comments:**

The terminal elimination phase of MK-0826 in blister fluid was unable to be characterized due to inadequate sampling. However, the data demonstrated that the half-life of MK-0826 in skin blister fluid may be greater than plasma. The sponsor did not comment on this finding, although it may be related to differences in protein binding between skin blister fluid and plasma, causing a reservoir effect or that healing of the skin blister basement membrane may have prevented the diffusion of drug from blister fluid back into the surrounding tissue.

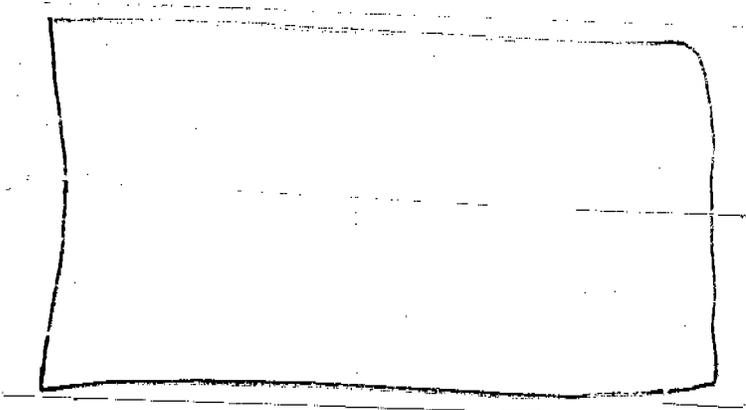
The protein binding of MK-0826 in skin blister fluid was not determined. Thus, the %T >MIC of unbound MK-0826 concentrations in skin blister fluid could not be calculated.

**Q. Does MK-0826 distribute into breast milk?**

The sponsor performed a lactation study (P023) to determine the penetration of MK-0826 into breast milk when administered intravenously to lactating women as well as determine the time required until MK-0826 is undetectable in breast milk after completing intravenous therapy. The lactation study was performed as a sub-study during a Phase 3 study investigating the efficacy of MK-0826 in women with acute pelvic infections. Five lactating women (5 to 14 days postpartum) received 1 g IV MK-0826 once daily for a minimum duration of 3 days and a maximum duration of 10 days.

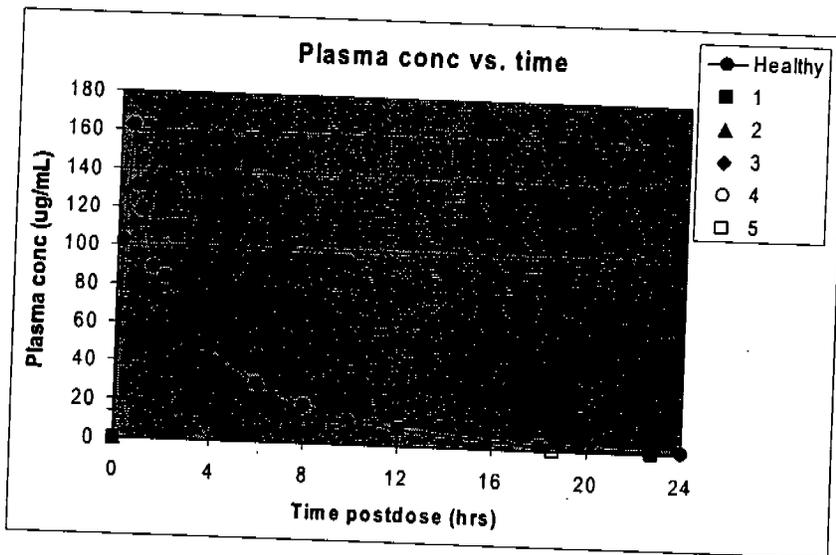
A single plasma sample was collected prior to the first dose of MK-0826 and another sample collected within the first 12 hrs of the last dose to coincide with the collection of a breast milk sample. A single breast milk sample was collected prior to the first dose of MK-0826 and a minimum of two additional breast milk samples were collected within the first 24 hrs of the last dose. The first sample was collected concomitantly with a plasma sample within 12 hrs of the last dose and the second breast milk sample was collected 12 to 24 hrs following the last dose. A morning breast milk sample was collected daily on days 2 to 5 following the last dose of study drug.

The plasma total MK-0826 concentrations predose and following the last dose of 1 gram IV MK-082 are shown in the table below.



A comparison between the plasma concentrations from five women with acute pelvic infections and healthy female subjects (study P009) is shown below.

Mean plasma concentration-time profile of total MK-0826 from healthy young female subjects (study P009) and individual MK-0826 plasma concentrations from five women with acute pelvic infections<sup>1</sup>



The plasma concentration from subject #3 at 2.7 hrs was less than anticipated, whereas the plasma concentration from subject #4 at 20.2 hrs was greater than anticipated. Since the pharmacokinetics of MK-0826 have not been investigated in patients with infections, it is unknown whether this represents an alteration in the pharmacokinetics in patients with acute pelvic infections or the sample times were inaccurately recorded.

MK-0826 concentrations in breast milk obtained pre-dose and for 5 days following the last dose of MK-0826 are shown below.

**MK-0826 concentrations in breast milk obtained pre-dose and for 5 days following the last dose of MK-0826**

Sample #	Subject 1		Subject 2		Subject 3		Subject 4		Subject 5	
	Time (hrs)	Conc (µg/mL)								
Predose	0.00	UND	0.0	NS	0.0	NS	0.0	NS	0.0	<0.125
Day 1A	22.8	0.30	9.5	0.37	2.7	0.23	20.1	0.19	18.8	<0.125
Day 1B	28.8	0.19	9.8	0.38	6.3	0.27	20.5	<0.125	22.8	<0.125
Day 2	49.8	UND	33.1	0.38	28.0	0.17	43.9	<0.125	46.7	UND
Day 3	70.3	UND	58.6	0.23	52.5	<0.125	66.5	<0.125	71.9	UND
Day 4	NS	UND	80.7	0.15	76.5	UND	96.5	UND	95.0	UND
Day 5	120.3	UND	104.8	<0.125	101.9	UND	117.5	UND	118.0	UND

Samples 1A and 1B were obtained within the first approximately 24 hours after the last dose of MK-0826. Samples 2, 3, 4, and 5 were obtained up to five days after the last dose.

UND - Undetectable

— Less than LOQ

NS - No sample was taken

The concentration of MK-0826 in breast milk within 24 hrs following the last day of therapy ranged from                     . By Day 3, the concentration of MK-0826 in breast milk was <0.125 µg/mL in four women, whereas the concentration of MK-0826 was <0.125 µg/mL in all five women by Day 5.

**Reviewer comments:**

Due to limitations in the study design, the sponsor was unable to calculate the percentage of the maternal dose that is transferred into breast milk. Calculation of a milk/plasma ratio (M/P) would allow for an estimation of infant exposure if the infant's daily milk consumption is known.

The reviewer approximated the M/P using corresponding milk and plasma concentrations at steady-state (Day 1A) and mathematical equations using physicochemical characteristics. Using corresponding milk and plasma samples, the mean M/P was 0.43 and ranged from                     . Using physicochemical characteristics, the estimated M/P (based on whole milk) using                      was 0.0484.

The amount of a drug excreted in breast milk can be estimated from the following equation:  
 Dose (mg) = average plasma concentration (µg/mL)/1000 \* M/P \* daily breast milk production (mL)

Assuming the average breast milk consumption by an infant is 150 mL/kg/day, a 5 kg infant will ingest the amount of MK-0826 shown in the table below.

M/P Ratio	Amount of drug excreted in breast milk (mg)	% of daily maternal dose excreted in breast milk
0.007	0.13 mg	0.013%
0.0484	0.87 mg	0.087%
1.667	29.8 mg	2.98%

An infant breast fed during MK-0826 therapy will likely ingest less than 1% of the maternal dose. However, the sponsor has not evaluated the safety of MK-0826 in breast feeding infants. Thus, if the mother chooses to wait until MK-0826 is no longer present in breast milk, breast feeding may resume

after three days following the last dose of MK-08726 and any breast milk collected prior to three days after the last dose should be discarded.

**APPEARS THIS WAY  
ON ORIGINAL**

---

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

13 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.