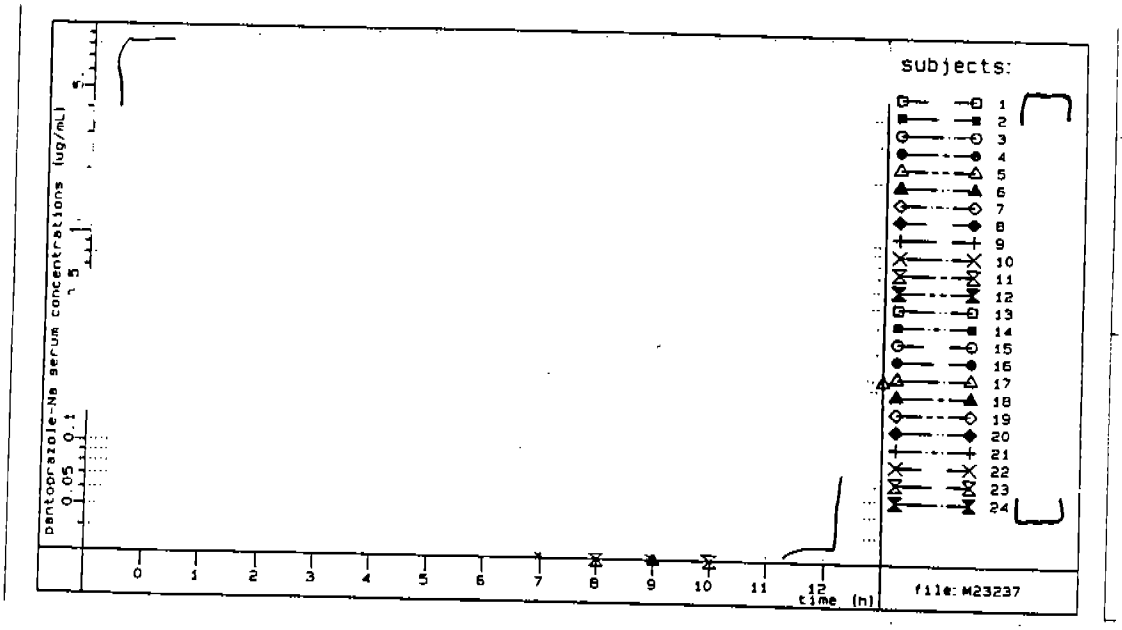
12. EFFECT OF FOOD ON PHARMACOKINETICS: The effect of food on the kinetics of oral enteric coated pantoprazole was evaluated in 24 healthy, overnight fasted volunteers (12 males and 12 females) who received a 40 mg dose followed by an additional 8-hour fast and just before a standard breakfast in a crossover fashion (Byk Gulden Protocol #FHP015; GMR-29715). Plots of individual subject serum concentration of pantoprazole versus time are presented in Figs. 21. The mean + SD pharmacokinetic parameters are presented in Table 15. Evidence of equivalence of pantoprazole systemic availability for the two treatments is presented in Table 16.

Fig. 21. Individual Subject Serum Concentration Profiles of Pantoprazole in in Normal Subjects Following a Single Dose of the 40 mg Enteric Coated Tablet (a) Under Fasted Conditions and (b) Just Before Breakfast

(a)



(b)

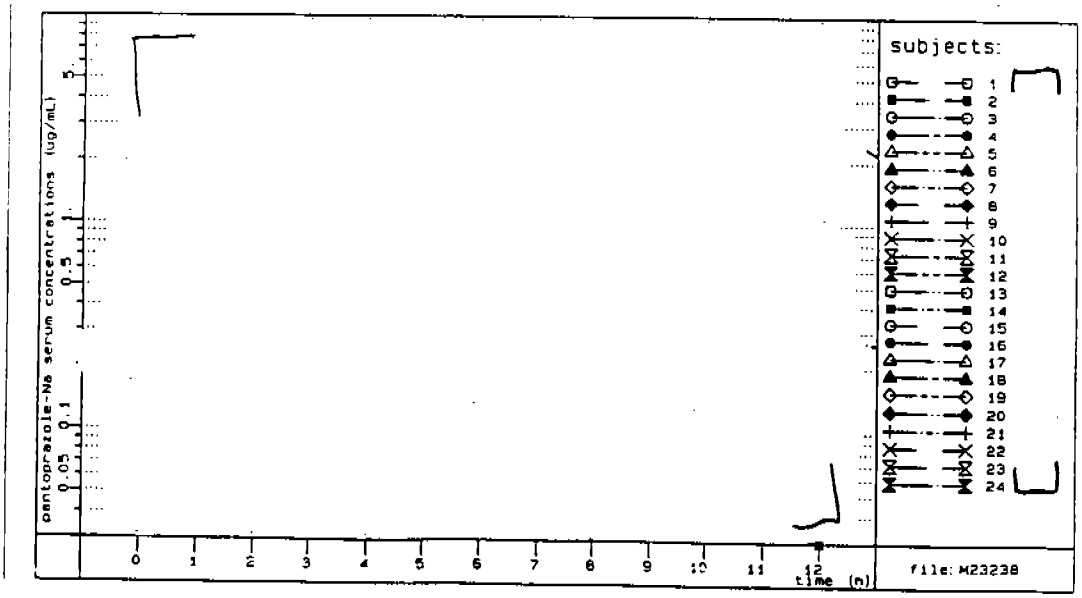


Table 15. Mean + SD Pharmacokinetic Parameters of Pantoprazole Following Single Oral 40 mg Enteric Coated Tablet Dose in Normal Subjects under Fasted Conditions and Just Before Breakfast

Protocol	n	Food/ No Food	Dose (mg)	C_{max} (ug/mL)	tlag (h)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)
FHP015	24	without food	40	2.72±1.03	1.6±0.7	2.7±0.7	6.2±4.4	1.4±0.5
GMR-29715	24	with food	40	2.58±1.09	3.0±3.3	3.9±3.6	5.0±3.3	1.3±0.6

Table 16. Assessment of Equivalence of AUC and Cmax of Pantoprazole Following a Single Oral Dose of the 40 mg Enteric Coated Tablet in Normal Subjects Administered under Fasted Conditions and Just Before Breakfast

Pantoprazole 40 mg p.o. Pharmacokinetic characteristic	Reference: without food Geometric mean, n=19 (n=23 for tmax-tlag) exp (mean(ln) ± SD (ln)) $)	Test: with food	Equivalence ratio (Test/Reference) Point estimate	90%-confidence interval after logarithmic transf.$)	
AUC(0,Inf.)(μgxh/mL)	4.696 (2.476, 8.905)	4.244 (2.445, 7.364)	0.90	0.803	1.016
Cmax (μg/mL)	2.378 (1.650, 3.427)	2.435 (1.552, 3.820)	1.02	0.86	1.22
$t_{½}$ (h)	1.337 (0.977, 1.831)	1.191 (0.798, 1.776)	0.89	0.81	0.98
tmax-tlag (h)	1.11 (0.28)	0.91 (0.49)	-0.20	-0.40	-0.01

$) mean (SD) for tmax-tlag, additive model (no transformation), confidence interval in hours

For the Two One-sided Test Procedure for the 90% confidence intervals, with the fasted treatment as reference and the fed treatment as test, the point estimate and the confidence limits of the ratio (test/reference) for log transformed mean C_{max} and AUC for the two treatments were within the interval of 0.80-1.25 required for equivalence. Therefore, the rate and extent of systemic availability of pantoprazole are considered to be equivalent when the drug is administered with or without food. The elimination half-life of pantoprazole was not affected by food. However, it needs to be noted that when given with food, t_{lag} and t_{max} of pantoprazole were longer and highly variable and so could the onset of drug effect. Thus, if predictable onset of drug effect is considered important, pantoprazole should be given in empty stomach.

13. EFFECT OF GENDER ON PHARMACOKINETICS: No studies were conducted to assess the effect of gender on the kinetics of orally administered pantoprazole enteric coated tablet per se. Thus, this reviewer re-analyzed the data for pantoprazole and its major metabolite, M2 in the food effect study above in order to generate this information. The results are summarized in Table 17. M and F in parentheses represents males and females, respectively.

Table 17. Assessment of Gender Differences in the Kinetics of Pantoprazole Following Single Oral Dose of the 40 mg Enteric Coated Tablet in Normal Subjects Administered under Fasted Conditions and Just Before Breakfast

Protocol FHP015 GMR-29715	n	Food/ No Food	Dose (mg)	C_{max} (ug/mL)	t_{lag} (h)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)
Pantoprazole								
	12 (M)	without food	40	2.39±0.83	1.6±0.6	2.7±0.7	5.0±3.3	1.4±0.6
	12 (F)	without food	40	3.00±0.97	1.5±0.8	2.6±0.8	7.3±5.1	1.4±0.4
	12 (M)	with food	40	2.27±0.72	3.0±2.8	3.8±3.1	4.9±3.4	1.4±0.8
	12 (F)	with food	40	2.91±1.34	2.9±3.8	3.9±4.3	5.0±3.4	1.1±0.3
M2								
	12 (M)	without food	—	0.62±0.28	1.8±0.5	2.8±0.5	1.6±0.5	1.4±0.5
	12 (F)	without food	—	0.60±0.24	1.5±0.7	3.0±0.8	1.6±0.3	1.6±0.6
	12 (M)	with food	—	0.57±0.27	3.2±2.8	4.3±3.4	1.4±0.3	1.2±0.3
	12 (F)	with food	—	0.53±0.25	2.4±3.4	3.5±3.8	1.3±0.4	1.3±0.4

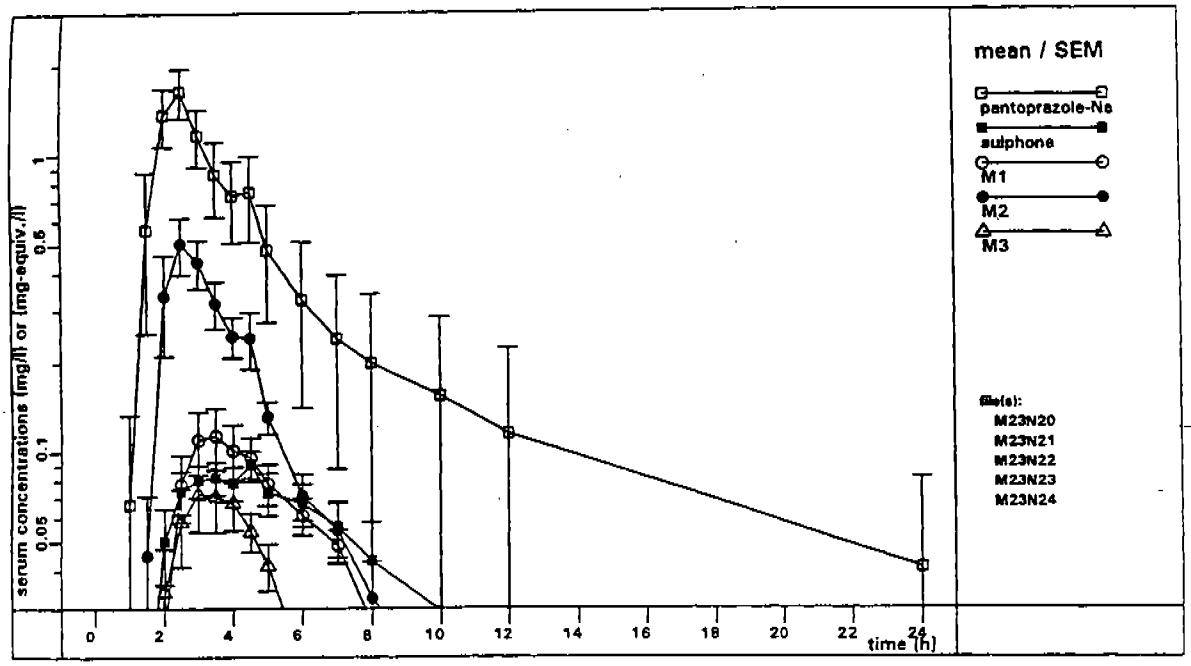
Pantoprazole t_{lag}, t_{max} and $t_{1/2}$ for males and females were comparable with or without food in the stomach. However, the mean C_{max} (without food), C_{max} (with food) and AUC (without food [not normalized for body weight]) for females were 25%, 28% and 46%, respectively, greater than the values for males. In both the males and the females, the major metabolite, M2 was efficiently eliminated. Therefore, it is considered that pantoprazole dosage adjustment for females is no necessary.

14. PHARMACOKINETICS IN SPECIAL POPULATIONS:

(a) Subjects with Impaired Renal Function: The effect of renal impairment on the kinetics of oral enteric coated pantoprazole was evaluated in Protocols FHP022E (GMR-29700) and FHP023 (GMR-31775) each evaluating a single oral 40 mg dose in 12 healthy, male subjects and 12 severely renally impaired, male subjects (SRI [Cl_{cr} =10-30 mL/min]). Plots of mean ± SD serum concentration of pantoprazole and of its major metabolite (M2) versus time are presented in Figs. 22 for these subject populations. The mean ± SD pharmacokinetic parameters for these moieties are presented in Table 18. PM and SRI in parenthesis represent poor metabolizers and severely renally impaired patients, respectively.

Fig. 22. Plots of Mean ± SEM Serum Concentration of Pantoprazole and Its Metabolites Versus Time in (a) Normal Subject and (b) Subjects with Severe Renal Impairment Following a Single Oral Dose of the 40 mg Enteric Coated Tablet

(a)



(b)

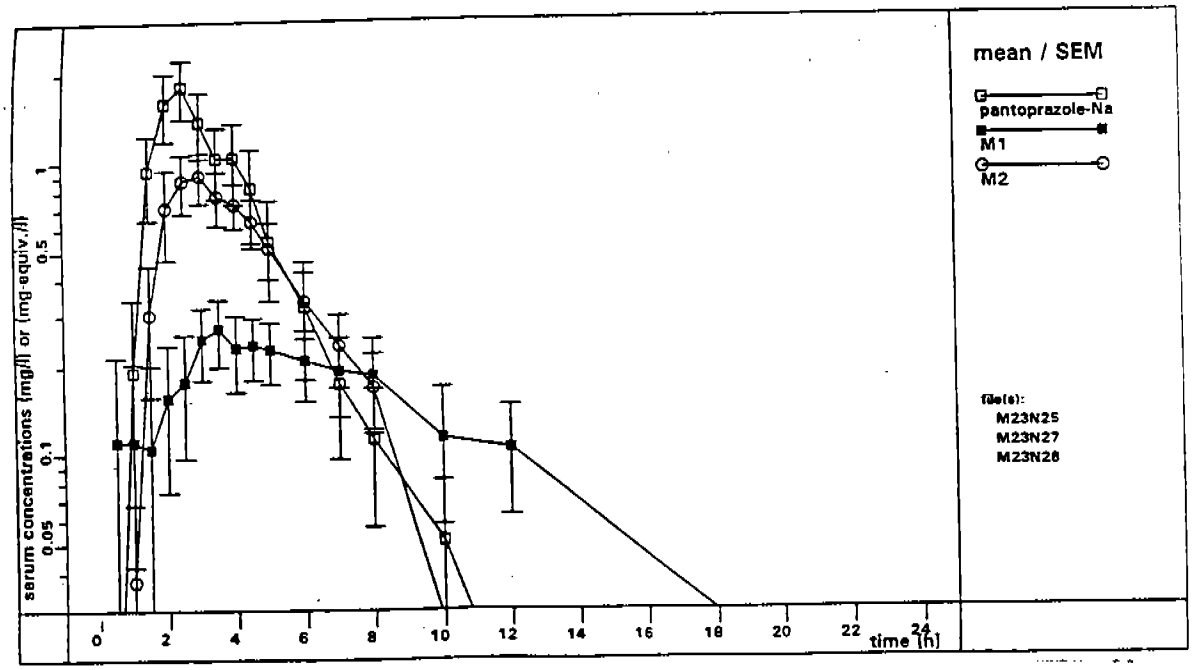


Table 18. Mean ± SD Pharmacokinetic Parameters of Pantoprazole and its M2 Metabolite Following Single Oral Dose of the 40 mg Enteric Coated Tablet Dose in Normal Subjects and Patients with Severe Renal Impairment

Protocol	n	Health Status	Dose (mg)	C_{max} (ug/mL)	t_{lag} (h)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)
PANTOPRAZOLE								
FHP022E	10	Normal	40	2.63±0.92	1.5±0.8	2.5±0.9	3.8±1.4	1.0±0.2
GMR-29700	2(PM)	Normal	40	4.61	1.0	1.5	24.8	3.6
				3.64	2.0	3.0	19.9	3.7
	12	SRI	40	2.30±1.01	1.1±0.6	2.2±0.8	5.3±3.9	1.4±0.7
FHP023	11	Normal	40	2.25±0.88	—	2.4±0.8	5.9±3.9	1.4±0.7
GMR-31775	1(PM)	Normal	40		—		38.6	8.6
	11	SRI	40	2.78±1.08	—	2.2±0.7	5.7±3.7	1.0±0.4
METABOLITE M2								
FHP022E	10	Normal	—	0.89±0.30	—	2.8±0.7	2.3±0.4	1.6±1.3
GMR-29700	1(PM)	Normal	—	0.19	—	3.5	—	5.3
	10	SRI	—	1.10±0.68	—	3.1±0.8	5.0±2.5	2.2±0.7
FHP023	11	Normal	40	0.72±0.35	—	2.6±0.7	1.5±0.5	1.3±0.5
GMR-31775	1(PM)	Normal	40	—	—	—	—	—
	11	SRI	40	1.12±0.48	—	2.8±0.8	2.3±0.9	1.6±0.6

These data suggest that in extensive metabolizers with normal or impaired renal function, pantoprazole is efficiently eliminated from the serum following oral administration of the 40 mg enteric coated tablet. Even in poor metabolizers ($t_{1/2} \leq 8.6$ h in these studies), significant drug accumulation would not occur upon multiple dosing (accumulation is 17% for $t_{1/2}$ of 8.6 h and once daily dosing). The sulfone metabolite and M3 were not quantified in the renally impaired subjects due to interference by co-eluting peaks. In Fig 22b, it is illustrated that on the average, the most persistent metabolite, M1 in the serum of the severely renally impaired subjects declines below the limit of quantification by 18 h postdose. Thus, like the parent drug, the metabolites of pantoprazole are efficiently eliminated from the serum in normal individuals as well as in individuals with severely impaired renal function. Based on these findings, pantoprazole dosage adjustment in renally impaired patients is considered unnecessary.

(b) **Subjects with Impaired Liver Function**: The single dose kinetics of pantoprazole was evaluated in 8 healthy, male subjects and 16 subjects with sonographically and clinically proven liver cirrhosis (8 patients with moderate hepatic impairment and 8 patients with severe hepatic impairment). Each subject received a single, oral dose of the 20 mg enteric coated tablet (Protocol FHP045E [GMR-32398]). The multiple dose kinetics of pantoprazole was evaluated in subjects with cirrhosis (n=14) receiving an oral dose of the 40 mg enteric coated tablet for 7 days and a 30 mg pantoprazole dose as an intravenous bolus injection for 5 days in a crossover study (FHP008E [GMR-31775]). Plots of mean ± SD serum concentration of pantoprazole (and metabolite, where detected) versus time for these studies are presented in Figs. 23 and 24. The mean ± SD pharmacokinetic parameters for these moieties are presented in Table 19. NV, MHI, SHI and LC in parentheses represent normal volunteer, moderate hepatic impairment, severe hepatic impairment and liver cirrhosis, respectively.

Fig. 23. Plots of Mean ± SEM Serum Concentration of Pantoprazole Versus Time in Normal Subjects and in Subjects with Moderate and Sever Hepatic Impairment Following a Single Oral Dose of the 20 mg Enteric Coated Tablet

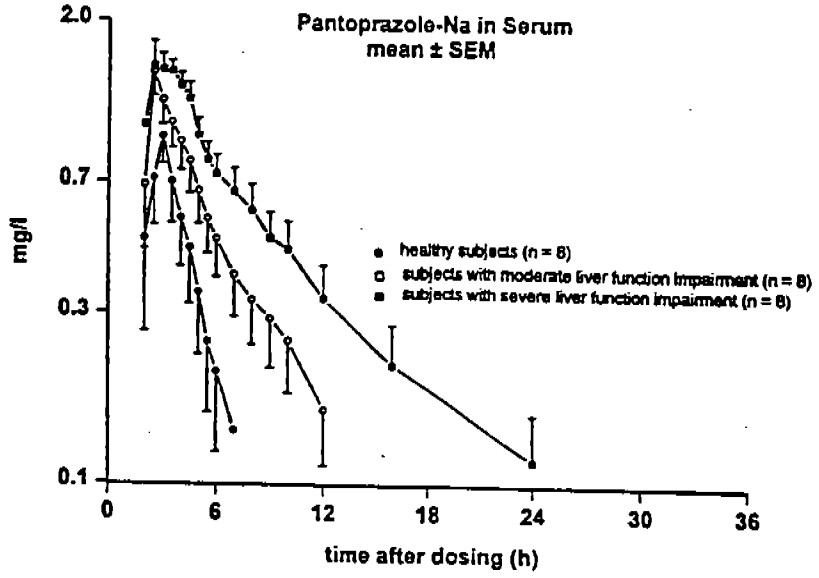


Fig. 24(a). Plots of Mean ± SEM Serum Concentration of Pantoprazole and its Sulfone Metabolite Versus Time in Subjects with Liver Cirrhosis Following a Daily Intravenous Dose of 30 mg for Five Days

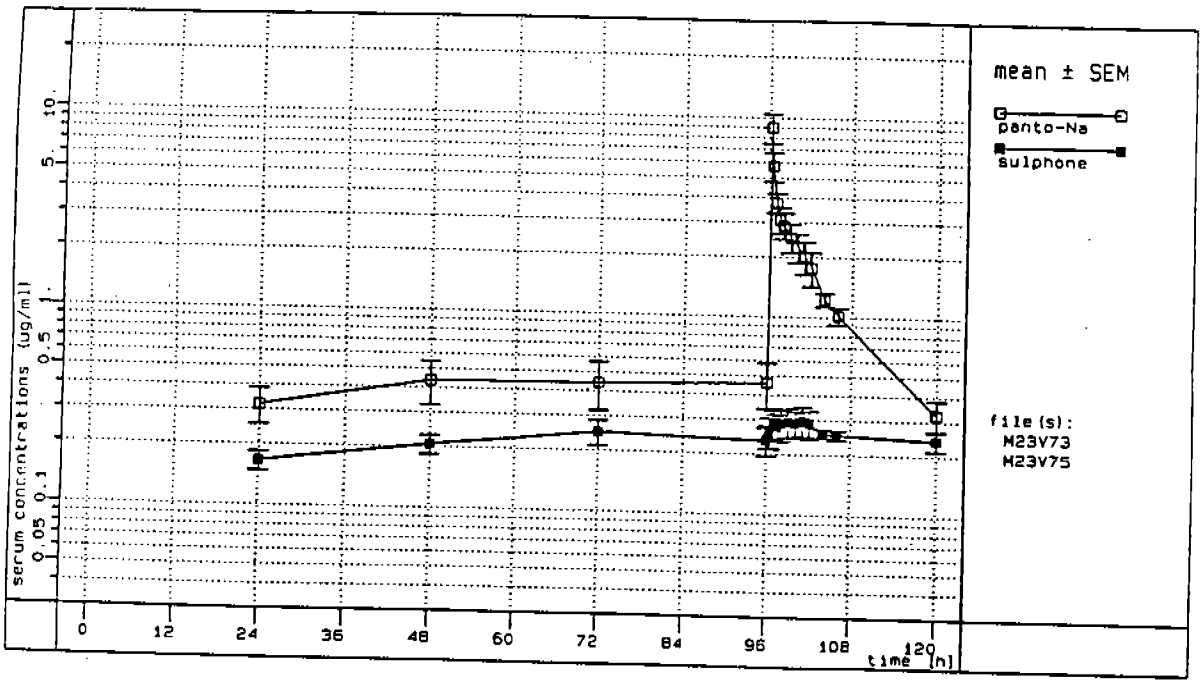


Fig. 24(b). A Plot of Mean ± SEM Serum Concentration of Pantoprazole and its Sulfone Metabolite Versus Time in Subjects with Liver Cirrhosis Following a Daily Oral Dose of the 40 mg Tablet for Seven Days

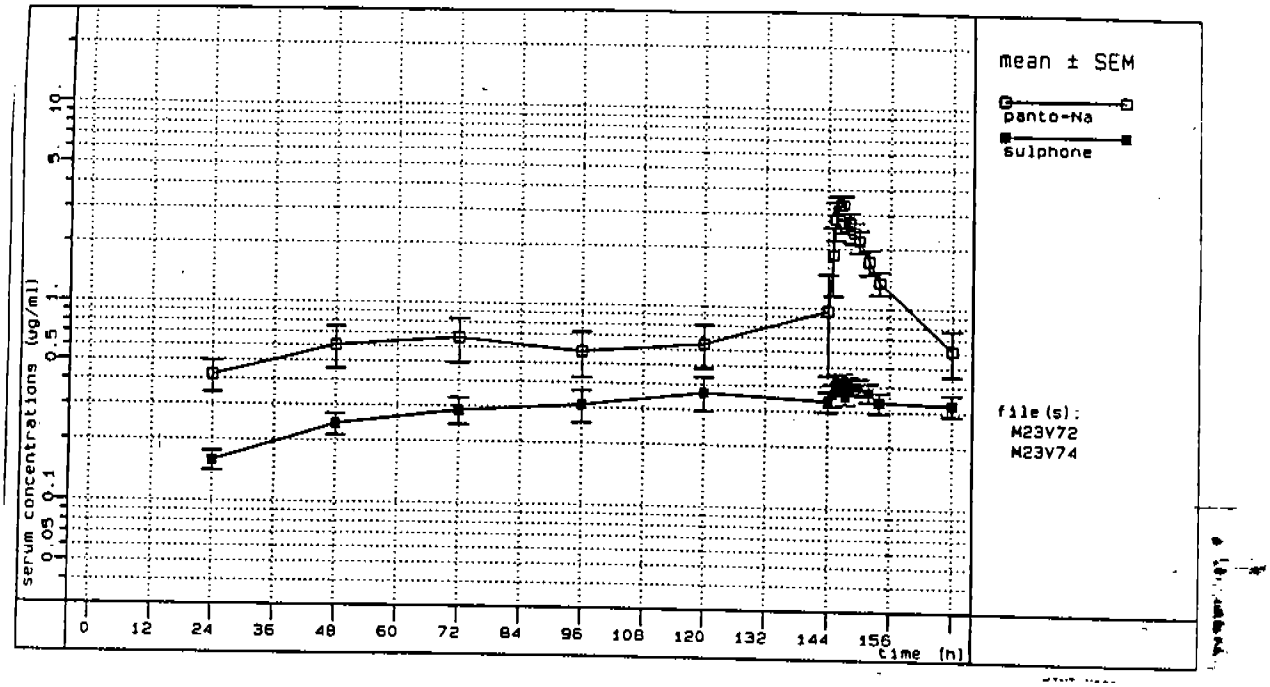


Table 19. Mean + SD Pharmacokinetic Parameters of Pantoprazole Following a single Oral 20 mg Enteric Coated Tablet in Nprmal Subjects and Patients with Moderate and Severe Hepatic Impairment and the Oral 40 mg Enteric Coated Tablet Dose or 30 mg Intravenous Dose in Patients with Liver Cirrhosis.

Protocol	Day	n	Dose (mg)	C_{max} (ug/mL)	$t'_{1/2}$ (h)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)	Cl_T	V_d
FHP045	1	8(NV)	20	1.35±0.24	—	2.4±0.7	3.4±3.0	1.6±1.4	—	—
	1	7(NV)*	20	1.31±0.23	—	2.4±0.7	2.4±1.1	1.1±0.4	—	—
	1	8(MHI)	20	1.75±0 31	—	2.3±0.7	7.0±3.5	3.3±1.8	—	—
	1	8(SHI)	20	1.96±0.25	—	2.4±0.6	12.3±6.2	6.0±3.0	—	—
FHP008E	7	12(LC)	40 (PO)	4.22±1.61	—	2.0±0.7	37±19	8.5±3.5	—	—
	5	12(LC)	30 (IV)	—	—	—	29±5.9	7.6±2.2	1.1±0.2	11.5±3.1

For the single, 20 mg dose regimen, the elimination half-life and AUC of pantoprazole increased significantly in the order of SHI > MHI > NV. Mild increases, in the same order, were also noted for C_{max}. For the multiple dose study in patients with cirrhosis, the mean (± SD) steady state C_{max} for the 40 mg oral dose (4.22±1.61 ug/mL [n=7]) was comparable to the mean value for the 80 mg oral dose in healthy, extensive metabolizers of pantoprazole (4.09±1.25 ug/mL [n=15], see page 11). In patients with moderate liver impairment and patients with severe liver impairment, individual subject elimination half-life ranged from 0.89 h to 5.3 h and from 1.78 h to 9.4 h, respectively. Based on these half-life values and a dosing interval of 24 h, significant drug accumulation is not expected in patients with moderate hepatic impairment upon multiple dosing. Subsequently, pantoprazole dosage adjustment is not necessary in this

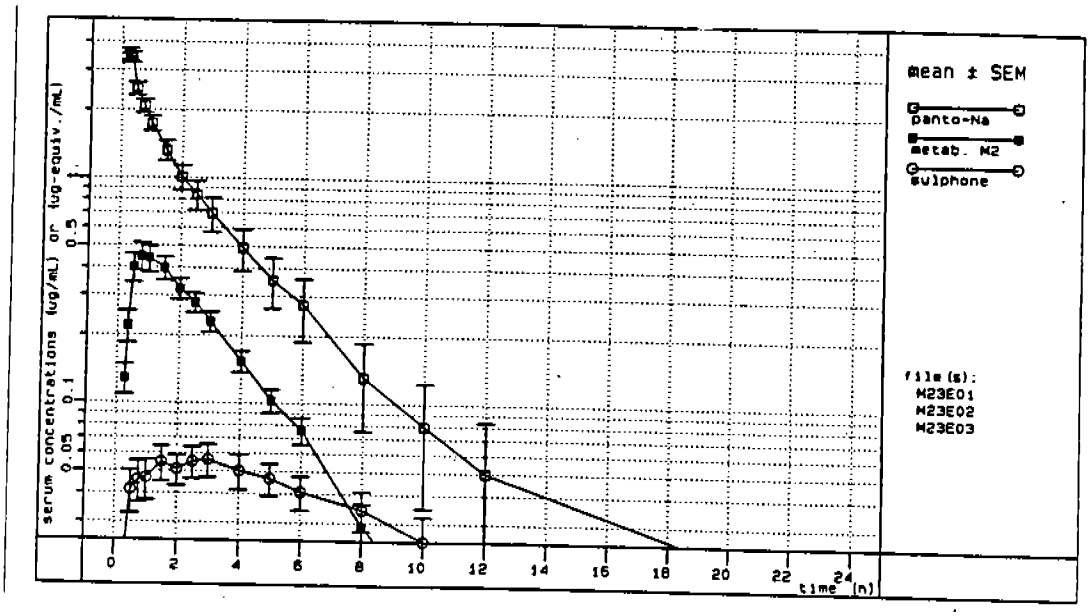
patient sub-population. For individuals with severe hepatic impairment, this reviewer has determined the individual subject half-life of 9.4 h in this study (the worst case scenario) would be associated with a steady state pantoprazole accumulation of 21%. In the drug product labeling, the sponsor indicates that dosage frequency should be reduced for patients with severe hepatic impairment. A dosing interval of 36-48 h has been calculated for this patient population by this reviewer (see Labeling Comment 6).

In Protocol FHP008E, following intravenous or oral administration of pantoprazole, M2, the major metabolite in individuals with normal liver function was not detected in blood in the serum of the patients with liver cirrhosis. Only the sulfone metabolite was detected. These data suggest that in liver cirrhosis, demethylation and sulfation processes in the metabolism of pantoprazole are significantly diminished leaving the CYP3A4 as the main operative isozyme. In this study, the absolute bioavailability of pantoprazole was 70% (versus 77% in individuals with normal liver function). The sponsor does not comment on the observed, reduced bioavailability of pantoprazole in this patient population. This could be related to prolonged residence of the drug in patients with liver cirrhosis resulting in a more extensive hepatic first pass effect mediated mainly by CYP3A4.

(c) **Elderly Subjects**: The single dose and multiple dose kinetics of pantoprazole was evaluated (i) in 15 healthy, elderly subjects (11 males and 4 females in the age range of 65 years to 76 years), who received a single, oral dose of the 40 mg enteric coated tablet for 7 days and a single dose of 30 mg by a 15-min intravenous infusion for 5 days in a crossover fashion (BYK Gulden Protocol FHP017E/2 [GMR-29733]) and (ii) in 16 healthy elderly subjects (12 males and 4 females also in the age range of 65 years to 76 years) who received the 40 mg enteric coated tablet dose daily for 7 days (Byk Gulden Protocol FHPO17E [GMR-29731]). Plots of mean $\pm$ SEM serum concentration of pantoprazole, M2 and the sulfone metabolite versus time are presented in Figs. 25-27. The mean $\pm$ SD pharmacokinetic parameters of pantoprazole are presented in Table 20. PM, IV and PO in parentheses represent poor metabolizer, intravenous administration and oral administration, respectively.

Fig. 25. Plots of Mean ± SEM Serum Concentration of Pantoprazole and its M2 and Sulfone Metabolites Versus Time in Healthy, Elderly Subjects on Day 1 (a) and Day 5 (b) Following a Daily Intravenous Dose of 30 mg for Five Days

(a)



(b)

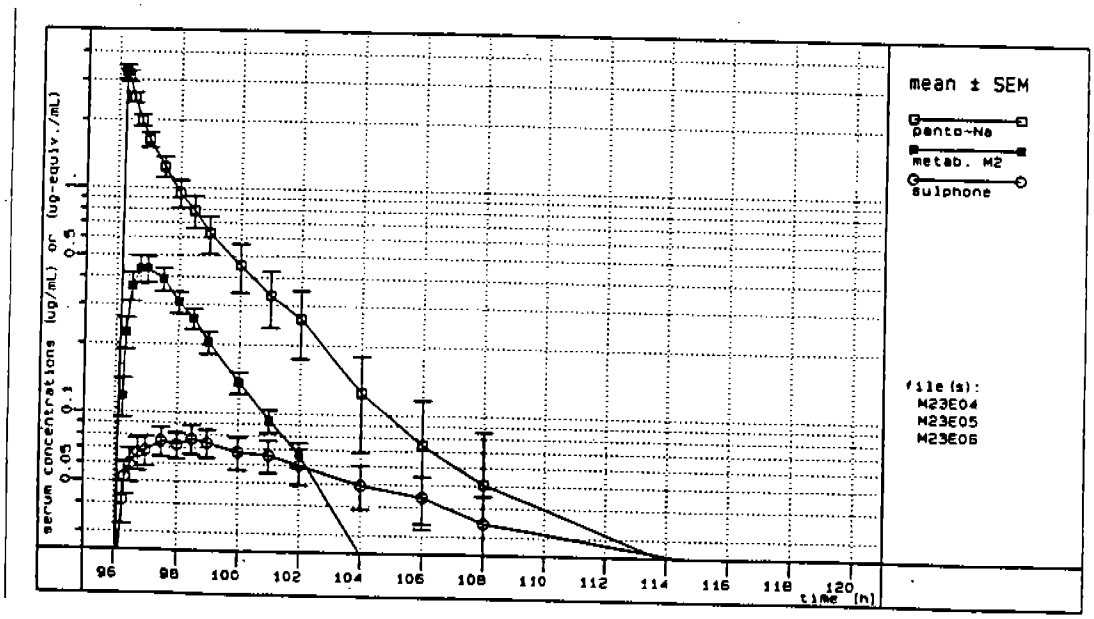
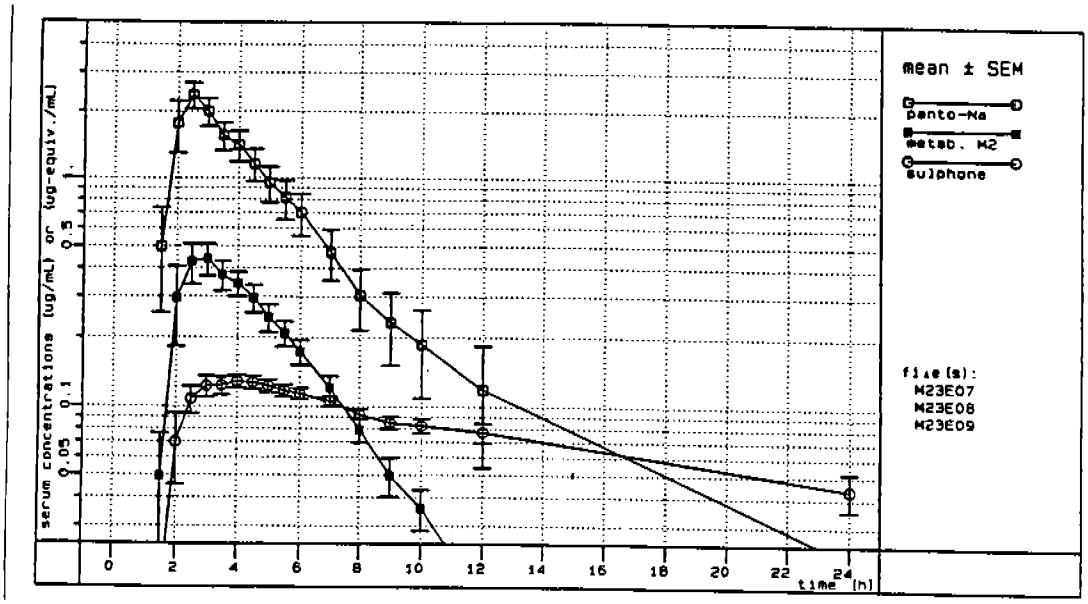


Fig. 26. Plots of Mean ± Serum Concentration of Pantoprazole and its M2 and Sulfone Metabolites Versus Time in Healthy, Elderly Subjects on Day 1 (a) and Day 7 (b) Following a Daily Oral Dose of 40 mg for Five Days (From Byk Gulden Protocol FHP017/E)

(a)



(b)

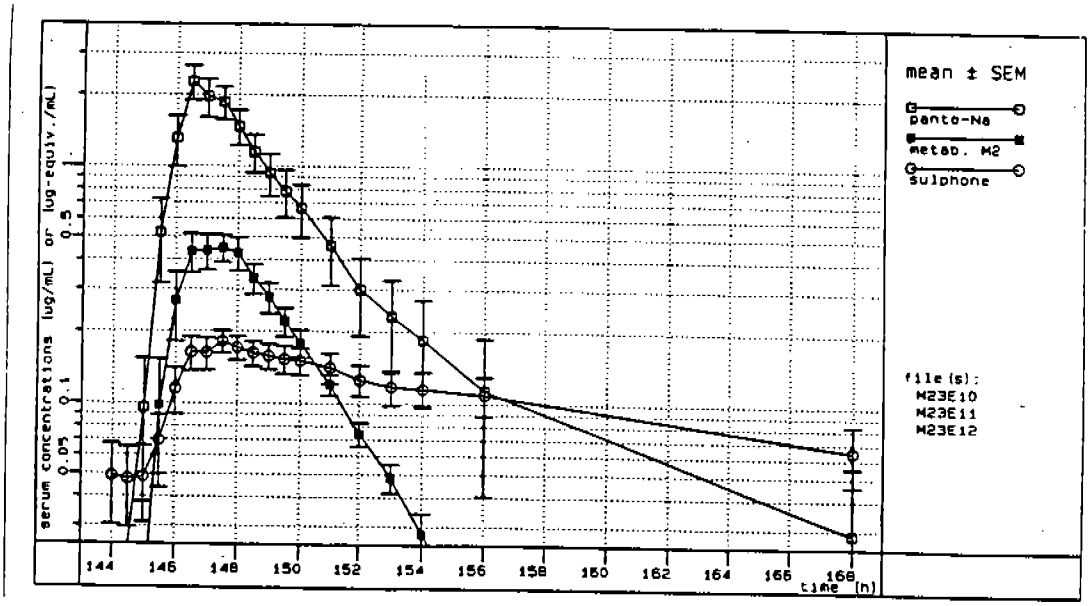
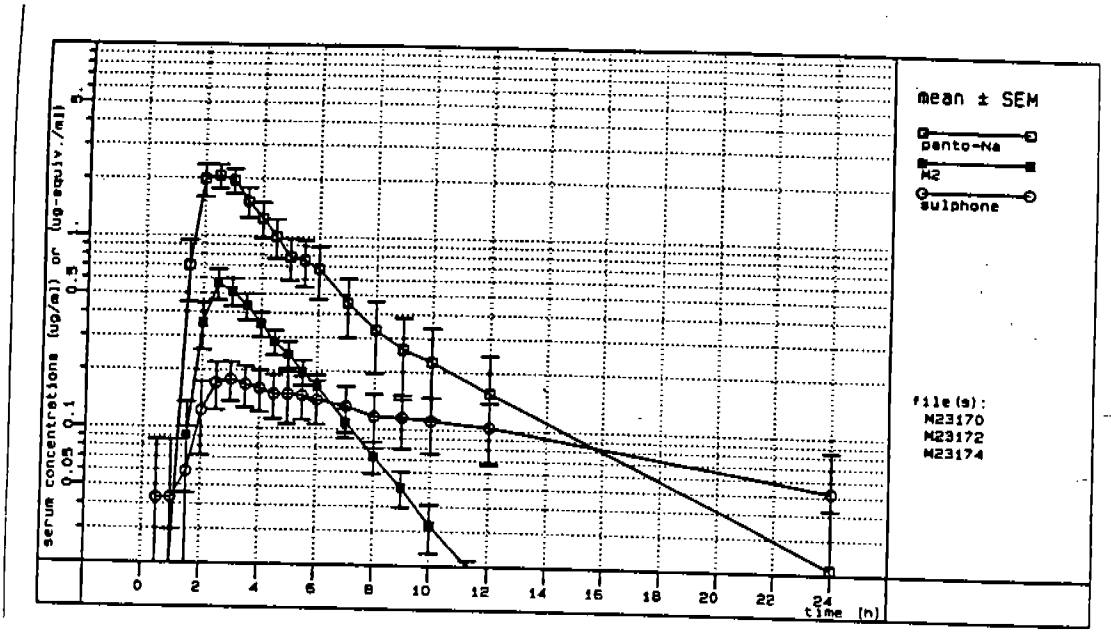


Fig. 27. Plots of Serum Concentration of Pantoprazole and its M2 and Sulfone Metabolites Versus Time in Healthy, Elderly Subjects on Day 1 (a) and Day 7 (b) Following Daily Intravenous Dose of 40 mg for Seven Days (From Byk Gulden Protocol FHP017E)

(a)



(b)

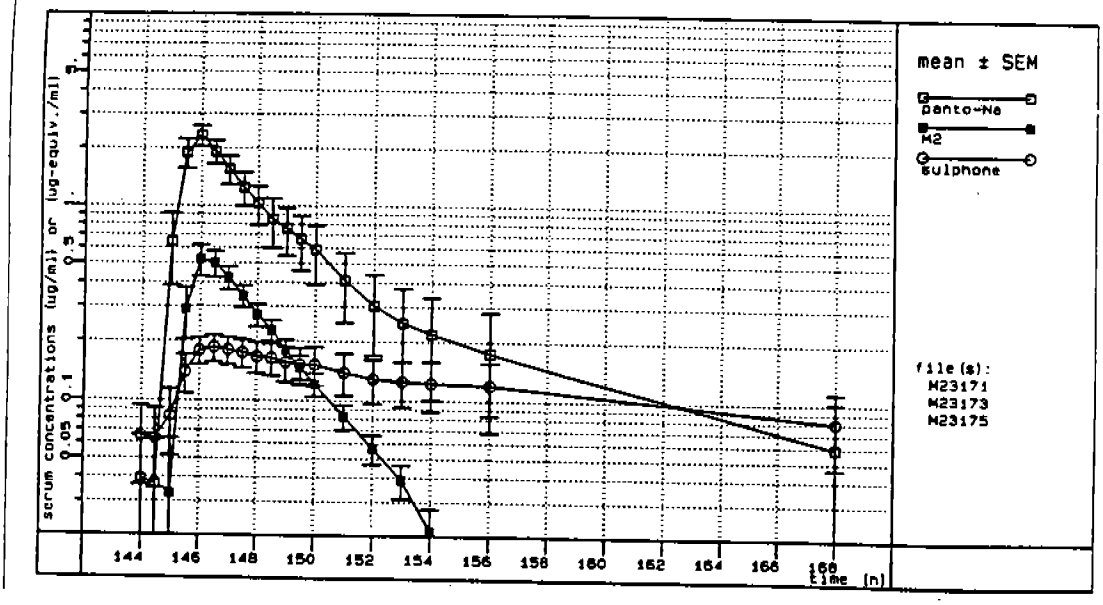


Table 20. Mean ± SD Pharmacokinetic Parameters of Pantoprazole Following Oral Doses of the 40 mg Enteric Coated Tablet for Seven Days and 30 mg doses by Intravenous Infusion for Five Days in Healthy Elderly Subjects

Protocol	Day	n	Dose (mg)	C_{max} (ug/mL)	t^{lag} (h)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)	Cl_T	V_d
FHP017/E	1	14	30(IV)	----	—	0.25	6.4±4.0	1.5±0.4	6.1±2.9	11.7±3.5
	1	1(PM)	30(IV)	----	—	0.25	18.8	5.5	1.59	
	5	14	30(IV)	----	—	0.25	5.6±2.9	1.5+0.5	6.6±2.4	12.4±2.8
	5	1(PM)	30(IV)	----	—	0.25	18.2	5.2	1.65	—
	1	14	40(PO)	3.12±1.23	0.7±2.9	2.7±1.1	7.6±4.2	1.5±0.5	—	—
	1	1(PM)	40(PO)	—	—	—	29.9	7.7	—	—
	7	14	40(PO)	3.30±1.7	—	2.5±0.7	7.4±4.5	1.5±0.6	—	—
	7	1(PM)	40(PO)	—	—	—	32.1	8.5	—	—
FHP017E	1	14	40(PO)	3.16±0.91	1.2±0.5	2.2±0.5	6.3±3.1	1.3±0.4	—	—
	1	1(PM)	40(PO)	—	—	—	30.2	7.9	—	—
	1	1(PM)	40(PO)				31.1	4.7		
	7	14	40(PO)	3.06±0.83	—	1.8±0.5	6.1±3.2	1.3±0.4	—	—
	7	1(PM)	40(PO)	—	—	—	29.0	7.7	—	—
	7	1(PM)	40(PO)	—	—	—	41.6	7.9	—	—

For each route of administration, the single dose and multiple dose kinetic data of pantoprazole were similar in each study. The oral dose kinetic data for the two studies were similar. For the 40 mg oral dose, the mean C_{max} and mean AUC appear to be somewhat greater than the values obtained for younger, healthy extensive metabolizers receiving the Phase IIb 2x20 mg tablets, the Phase III clinical study 40 mg tablet, the to-be marketed 40 mg tablet and the newly developed 40 mg tablet (Cmax: ——— ug/mL; AUC: ——— [mg/mL]h; see Table 5). However, since $C_{max(dose\ \#1)}$ approximately equals $C_{max(dose\ \#7)}$, drug accumulation does not occur upon multiple dosing. Thus, no pantoprazole dosage adjustment is necessary in elderly patients.

Two pantoporazole metabolites (M2 and the sulfone) were quantified in these studies. Following intravenous administration, M2 serum exposure > sulfone serum exposure, however, in both oral studies, sulfone serum exposure > M2 exposure (see Figs. 25-27). These findings suggest, once again, the pre-eminence of CYP3A4 in mediating hepatic first pass metabolism. Furthermore, in the oral studies, the serum concentration of the sulfone metabolite remained above the limit of detection at 24 h postdose. This is not expected to be associated with any significant safety problem as this metabolite is said to be inactive.

(d) **PEDIATRICS**: No studies were conducted to determine the kinetics of pantoprazole in the pediatric population. In the drug product labeling, it is stated, under "Pediatric Use", that "safety and effectiveness [of pantoprazole] in children have not been established".

15. DRUG-DRUG INTERACTIONS:

(a) Effects of Co-administered Drugs on the Kinetics of Pantoprazole: Pantoprazole is metabolized by the CYP_{450} isozymes, predominantly by CYP2C19. The other CYP_{450} isozymes (CYPs 3A4, 2D6 and 2C9) play only minor roles in the metabolism of the drug. Therefore, regarding pantoprazole metabolism, inhibition of CYP2C19 would be of greatest concern. Based on the list of CYP_{450} isozyme substrates provided by the Clinical Pharmacology Division ——————————————— as updated on April 16, 1999, the only CYP2C19 inhibitors currently used in clinical practice are fluoxetine, fluvoxamine, ketoconazole, lansoprazole, omeprazole and triclopidine. This document lists no inducers of CYP2C19 at this time. The sponsor determined, in an *in vitro* study using human liver microsomes, that ketoconazole reduced the metabolism of pantoprzole by 35% (see item 4(c) [page 21). Fluoxetine, fluvoxamine and triclopidine were not evaluated by the sponsor *in vitro* or *in vivo*. Evaluation of lansoprazole and omeprazole would not be necessary as these are therapeutic alternatives and would not be administered concomitantly. However, the interactions of other substrates of CYP2C19 (diazepam [also substrate of CYP3A4] and phenytoin [also an inducer of CYP3A4]), nifedipine (a substrate of CYP3A4) and diclofenac (a substrate of CYP2C9) were evaluated in normal volunteers receiving pantoprazole with and without the co-administered drugs in crossover studies. Also evaluated in similar studies for possible interactions with pantoprazole were digoxin and the antacid, Maalox™. For each study, the protocol number and a summary of the pharmacokinetic parameters of pantoprazole are presented in Table 21. The co-administered drug was administered orally unless otherwise indicated. P, C, S, PM, IV and PO in parentheses represent pantoprazole, with co-administered drug, without the co-administered, poor metabolizer, intravenous administration and oral administration, respectively.

Table 21. Mean ± SD Pharmacokinetic Parameters of Pantoprazole with and without Concomitantly Administered Drugs

Protocol	Day	n	Dose(P) (mg)	C_{max} (ug/mL)	t_{lag} (h)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)	Cl_T	V_d
Diazepam (0.1 mg/ kg[IV])										
FHP004	3	12(S)	240(IV)	—	—	0.25	48±12	1.2±0.1	5.3±1.3	9.3±2.3
	4	12(C)	240(IV)	—	—	0.25	47±13	1.2±0.1	5.5±1.6	9.7±3.6
Phenytoin (3000 mg) FHP026E										
	1	23(S)	40(PO)	2.53±0.64	1.9±1.0	2.8±1.1	4.9±1.7	1.3±0.2	—	—
	4	23(C)	40(PO)	2.66±0.55	1.4±0.8	2.3±0.8	5.5±1.4	1.4±0.3	—	—
Nifedipine (20 mg)										
FHP025	5	23(S)	40(PO)	2.40±0.96	1.4±0.9	2.5±0.8	4.6±2.7	1.2±0.3	—	—
	5	1(S[PM])	40(PO)				26	9.6	—	—
	10	23(C)	40(PO)	2.81±0.83	1.5±0.8	2.5±0.5	4.6±2.7	1.2±0.3	—	—
	10	1(C[PM])	40(PO)				28	9.2	—	—

Table 22 (contd.). Mean ± SD Pharmacokinetic Parameters of Selected Drugs with and without Concomitant Administration of Pantoprazole

Warfarin (25 mg)									
R-Warfarin									
FHP012E	2	26(S)	40(PO)	1.5±0.2	4.2±2.7	97±29	46±10	—	—
	2	26(C)	40(PO)	1.5±0.2	4.1±3.1	100±56	47±10	—	—
S-Warfarin									
FHP012E	2	26(S)	40(PO)	1.4±0.2	3.0±2.1	54±18	29±8	—	—
	2	26(C)	40(PO)	1.4±0.2	3.1±1.7	56± 21	31±8	—	—
Metoprolol (95 mg)									
R-Metoprolol									
FHP035	5	18(S)	40(PO)	23±14	3.9±5.3	380±267	—	—	—
	5	18(C)	40(PO)	23±12	2.8±1.0	362±250	—	—	—
S-Metoprolol									
FHP035	5	18(S)	40(PO)	29±15	4.1±5.2	490±298	—	—	—
	5	18(C)	40(PO)	29±13	2.9±1.0	468±282	—	—	—
Nifedipine (20 mg)									
FHP025	5	24(S)	40(PO)	55±21	1.2±0.4	250±97	4.8±1.4	—	—
	10	24(C)	40(PO)	56±24	1.3±0.4	272±122	5.4±2.2	—	—
Diclofenac (100 mg)									
FHP030	1	24(S)	40(PO)	2.5±1.1	2.5±1.3	3.2±0.7	2.3±2.3	—	—
	1	24(C)	40(PO)	2.4±0.7	2.1±0.8	3.3±0.8	2.0±0.9	—	—
Digoxin (0.2 mg/bid)									
FHP019	1	18(S)	40(PO)	2.1±0.5	0.9±0.4	12.5±2.8	—	—	—
	5	18(C)	40(PO)	2.3±0.6	1.1±0.4	13.8±2.6	—	—	—
Theophylline (700 mg [IV$_{inf}$])									
FHP006E	1	8(S)	40(PO)	12.4±2.4	1.5±2.7	186±28	6.7±1.3	—	—
	4	8(C)	40(PO)	12.5±1.5	1.6±3.0	178± 42	6.0±1.4	—	—
Cisapride1 (20 mg)	1	16(S)	40(PO)	57.5±15	1.7±0.4	483±266	6.7±4.5	—	—
P102	1	16(C)	40(PO)	47.9±12	1.4±0.4	409±195	6.8±4.8	—	—

The kinetics of substrates of CYPSs 2C19 (diazepam [also substrate of CYP3A4], phenytoin [also an inducer of CYP3A4] and R-warfarin), 3A4 (nifedipine), 2D6 (metprolol) and 2C9 (diclofenac) were not significantly affected by co-administration of pantoprazole. The C_{max} and AUC of desmethyldiazepam, an active metabolite of diazepam were also not affected by pantoprazole. Based on these findings, the kinetics of other drugs metabolized by these isozymes is not expected to be significantly affected by pantoprazole. Therefore, adjustment of the doses of such drugs for patients concomitantly treated with pantoprazole is not necessary.

Cisapride is used in the treatment of disorders of gastric hypomotlilty. The data presented in the Table 22 above suggest that upon co-administration with pantoprazole, the mean C_{max} and mean AUC of cisapride decreased by 17% and 15%, respectively but its mean t_{max} and mean $t_{1/2}$ were not significantly altered. The sponsor considers these pharmacokinetic changes as minor and not clinically relevant. The sponsor further states that the slight decrease in cisapride C_{max} resulting from pantoprazole coadministration would be advantageous as it would help minimize cisapride concentration-related adverse events. Thus, is considered that adjustment of cisapride dosage in patients concomitantly treated with pantoprazole is not necessary.

The effect pantoprazole on the kinetics of two frequently used drugs with narrow therapeutic ranges (digoxin and theophylline) was also evaluated and was considered insignificant. However, the mild increases in mean C_{max} (9.5%) and mean AUC (10.4%) of digoxin need to be noted. It would be prudent to monitor patients on concomitant digoxin and pantoprazole therapy in clinical settings in order to assess the clinical significance of the observed changes in these digoxin pharmacokinetic parameters an, subsequently, the need for digoxin dosage adjustment in patients concomitantly treated with pantoprazole [see Labeling Comment 9(b)(iii)].

16. SAMPLE ANALYSIS: In the studies evaluating the kinetics of unlabeled pantoprazole and its metabolites, serum sample analysis was performed by ——— Across studies, pantoprazole LOQ ranged from ——— ug/mL, within-day precision ranged from ——— between-day precision ranged from ——— and accuracy (recovery from biological matrix) ranged from ——— for serum/plasma samples. The metabolites were adequately separated from one another and from the parent drug. Synthetic samples of the metabolites (except for the sulfone metabolite in some cases) were generally not available. Thus, the metabolites were semiquantitatively evaluated (as mg equivalents of pantoprazole).

In the study evaluating ^{14}C-labeled pantoprazole, the amount of ^{14}C-radioactivity was determined by counting ——— analyzer for 10 min (whole blood and serum samples) or 15 min (urine and feces samples). The mean$\pm$SD counting efficiency of the analyzer was 96.6$\pm$0.29% (n=11) for whole blood and serum samples and 96.6$\pm$0.19% (n=11) for urine and feces samples. Background ranged from 20.3 dpm (disintergations per minute) to 24.0 dpm for whole blood and serum samples and from 21.0 dpm to 24.0 dpm for urine and feces samples. The limit of detection was taken to be — dpm and LOQ was — dpm. The ^{14}C-radioactivity in each matrix $\leq$ 70 dpm. For each matrix, both intra-day and inter-day reproducibility CVs were $\leq$7.1%% (except for whole blood and serum intra-day and inter-day values of 9.3% at 71 dpm and 10.1% at 70 dpm, respectively). The accuracy of the analytical method $\geq$ 93.4% for each matrix analyzed.

17. PHARMACOKINETIC ANALYSIS: For each study, the pharmacokinetic parameters of pantoprazole were satisfactorily determined using standard pharmacokinetic equations, based on the pharmacokinetic model in use (compartmental or noncompartmental model).

18. DRUG FORMULATION: The compositions of the to-be-marketed formulation (Formulation E), Phase III clinical study formulation (Formulation C) and the Phase IIb clinical Study Formulation (Formulation B) are presented in Table 23.

Table 23. Pantoprazole Drug Product Compositions for the To-be-marketed Formulation and the Phase III and Phase IIb Clinical Study Formulations

Ingredient	B	C	E
Pantoprazole (mg)	20	40	40
Sodium carbonate (mg)			
Mannitol (mg)			
Povidone (mg)			
Crospovidone (mg)			
Calcium Stearate			
HPMC (mg)			
Povidone (mg)			
Titanium dioxide (mg)			
Propylene glycol (mg)			
Yellow Ferric oxide (mg)			
Aqueous solution of;			
Triethyl citrate (mg)			

The to-be-marketed formulation and the Phase III clinical study formulation differed only in the spray patterns of the enteric coating material due to the use of a larger scale equipment in the production of the to-be-marketed formulation. This may have caused slight differences between the two formulations in the amounts of enteric coating material per tablet.

19. DISSOLUTION TESTING: The dissolution characteristics of pantoprazole were evaluated based on Method B, USP <724> for delayed release (Enteric Coated Articles), using Apparatus 2 (paddle). The testing specifications were the same as those outlined in Table 24. A summary of the results for the pantoprazole tablets used in the bioequivalence studies is presented in Table 25.

Table 24. Proposed Pantoprazole Enteric Coated Tablet Dissolution Method and Specifications.

Dosage Form	Enteric Coated Tablet
Strength:	40 mg
Apparatus Type:	USP Apparatus 2
Media:	Acid Stage: 0.1N HCl
	Buffer Stage: pH 6.8 Phosphate Buffer
Volume:	1000 mL
Speed of Rotation:	100 RPM
Sampling Time:	Acid Stage: 2 hours
	Buffer Stage: 45 minutes
Analytical Method:	Ultraviolet spectrophotometry
	Acid Stage: 305 nm
	Buffer Stage: 288 nm
Recommended Dissolution Specifications:	Acid Stage: not more than 10% released
	Buffer Stage: — (Q) ———

Table 25. Dissolution Results for Pantoprazole Enteric Coated Tablets Used in the Bioequivalence Studies.

Biostudy	Formulation	Strength	Batch	Stage	Collection Time (minutes)	Mean % Released
A9915-GER	B	20mg	4/1/1	Acid	120	Conforms
				Buffer	45	90.9
FHP014	B	20mg	4/1/2	Acid	120	Conforms
				Buffer	45	97.9
FHP014	C	40 mg	EA164	Acid	120	Conforms
				Buffer	45	105.9
FHP028	C	40mg	3-6-0	Acid	120	Conforms
				Buffer	45	102.5
FHP028	E	40 mg	493180	Acid	120	Conforms
				Buffer	45	96.0
FHP041	E	40 mg	494480	Acid	120	Conforms
				Buffer	45	102.9
FHP041	F-40	40 mg	495150	Acid	120	Conforms
				Buffer	45	98.3
FHP042	F	20 mg	395040	Acid	120	Conforms
				Buffer	45	103.5
FHP042	G	20 mg	396170	Acid	120	Conforms
				Buffer	45	98.9

For all enteric coated formulations tested, the buffer phase dissolution amount, Q $\geq$ _____ was met. The sponsor states that the acid phase dissolution amount also conformed to the specification, "not more than 10%" of pantoprazole released from tablet in 2 h.

LABELING COMMENTS

The following comments relate to the Clinical Pharmacology section of the drug product labeling:

1. Under the sub-section, **Pharmacokinetics**, the portion, "Peak serum concentration (C_{max}) ... are unaltered with multiple dosing" should be replaced with the following:

> Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers with normal liver function receiving an oral dose of the enteric coated 40 mg pantoprazole tablet, the peak concentration (C_{max}) is —— ug/mL, the time to reach the peak concentration (t_{max}) is 2.4 h, the total area under the plasma concentration versus time curve (AUC) is 4.8

2. Under the sub-section, **Absorption**, the statement, ——— should be replaced with the following:

> Pantoprazole absorption is not significantly affected by concomitant administration of antacids ———

3. The information provided under the sub-section, **Distribution** should be replaced with the following:

4. The information provided under the sub-section, **Metabolism** should be replaced with the following:

5. The information provided in the sub-section, **Elimination**, should be replaced with the following.

6. Under the sub-section, **Hepatic Impairment**, the statement, ' should be replaced with the following:

7. A sub-section entitled, **Drug-Drug Interactions** should be included in the **Clinical Pharmacology** section of the drug product labeling. Under this sub-section, the following information should be provided:

8. In the **Dosage and Administration Section**, under the sub-section, **Treatment of Erosive Esophagitis**:

(a) The following statement should constitute the second paragraph:

[redacted]

(b) The statement, [redacted] should be deleted from the next (now third) paragraph.

(c) The following should be inserted as the fourth paragraph:

[redacted]

(d) The statement, "PROTONIX enteric coated tablets should be swallowed whole ..... concomitantly with PROTONIX" should be modified as follows:

PROTONIX enteric coated tablet should be swallowed whole, [redacted] with or without food in the stomach. [redacted] Concomitant administration of antacids does not affect the absorption of PROTONIX.

9. In the **Precautions** section:

(a) Under the sub-section, **Information for Patients,** the statement, "The tablets should be swallowed whole ..... [redacted] should be modified as follows:

The tablet should be swallowed whole, [redacted] with or without food in the stomach. [redacted] Concomitant administration of antacids does not affect the absorption of pantoprazole.

(b) Under the sub-section, **Drug Interactions**:

(i) The last statement in the first paragraph, **"There was no interaction with concomitantly administered antacids"** should be preceded by the following:

Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when co-administered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary.

(ii) The following statement should constitute the second paragraph:

[

]

(iii) The following should constitute the third paragraph:

[

]

The last paragraph under this sub-section should be retained.

GENERAL COMMENTS

1. In the proposed drug product labeling, under the sub-section, **Enterochromaffin-Like (ECL) Cells**, the sponsor states the following:

[ ]

Do these findings raise any safety concerns about the short term and/or long term use of pantoprazole?

2. In evaluating the toxicology of pantoprazole in animals, it was noted that the (-)-enantiomer is more toxic than the (+)-enantiomer. However, development of only the (+)-enantiomer for marketing has not been recommended in this review since it has also been noted that *in vivo*, the (+)-enantiomer readily converts to the (-)-enantiomer.

OVERALL COMMENTS

1. In assessing the dissolution profile of the 40 mg enteric coated pantoprazole tablet, USP Apparatus 2 at a rotation speed of 100 rpm was utilized (NDA Vol. 1.08 [page 114]). Usually, with this apparatus, the recommended rotation speed is 50-75 rpm. It is requested that the dissolution profile at the recommended rotation speed (50-75 rpm) be submitted to the Agency.

2. For the acid (resistance) phase of Dissolution Testing for which the drug release limit is set at $\leq$ 10%, the results are provided only for the 2-hour time point and are stated simply as **"conforms"** (NDA Vol. 1.108 [page 113]). It is recommended that the actual drug release data from which conformity was concluded be provided as was the case with the buffer stage of dissolution testing (see NDA Vol. 1.108 [page 112]).

RECOMMENDATION

NDA 20-987 for pantoprazole sodium (Protonix™) enteric coated tablets submitted by the sponsor on June 30, 1998 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. From a pharmacokinetic perspecrive, the NDA is considered approvable. However, the issues raised in Labeling Comments 1-9 (pages 49-53) and Overall Comments 1-2 (page 53) need to be satisfactorily addressed by the sponsor.

Please convey this Recommendation, Labeling Comments 1-9 (pages 48-52) and Overall Comments 1-2 (page 53), as appropriate, to the sponsor. General Comments 1-2 (page 53) should be brought to the attention of the reviewing medical officer.

/S/ 06/25/99

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by David Lee, Ph.D. /S/ 6/28/99

FT Initialed by David Lee, Ph.D. /S/ 6/28/99

Clinpharm/Biopharm Briefing: 06/24/99 [Attendees: Selen (HFD-880), Ajayi (HFD-880), Fossler (HFD-870), Suliman (HFD-870), M. Chen (HFD-870), Hunt (HFD-870)].

cc: NDA 20-987, HFD-180, HFD-180 (Walsh), HFD-870 (M. Chen, Hunt, Lee and Udo), CDR (Attn: Barbara Murphy).