CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20988

<u>CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)</u>

original in 20-988 binder

NDA 20-987 SUBMISSION DATE: 06/30/98

PANTOPRAZOLE SODIUM TABLET
PROTONIX™ JUN 28 1999
40 MG ENTERIC-COATED TABLET → NOT I.V.!

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TYPE OF SUBMISSION: ORIGINAL NDA: NEW MOLECULAR ENTITY (NME)

SUBMISSION CODE: 1S

CONTENT PAGE

1. SYNOPSIS/BACKGROUND

NDA 20-987 for pantoprazole sodium (Protonix™) 40 mg enteric-coated tablet was submitted by the sponsor on June 30, 1998. Protonix™ is proposed for short-term treatment (4-8 weeks) of erosive esophagitis associated with gastroesophageal reflux. In the drug product labeling, it is stated that "for those patients who have not healed after eight weeks of treatment, an additional 8 week course of PROTONIX™ may be considered". The 40 mg strength was selected for marketing in that in clinical studies, it was significantly more efficacious than the 10 and 20 mg strengths but was similar in efficacy to the higher strengths tested (60, 80 and 120 mg). Pantoprazole acts by non-competitive inhibition of the proton pump via covalent binding to the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell.

Based on the information provided in the drug product labeling, benign and malignant neuroendocrine (NE) cell tumors of the gastric fondus and hyperplasia of enterochromaffin-like (ECL) cells were observed in male and female rats treated with Protonix™ doses $\geq$15 mg/kg/day and $\geq$0.5 mg/kg/day, respectively, for 24 months. The labeling recommended dose of Protonix™, 40 mg/day amounts to 0.57 mg/kg/day in a 70 kg individual. ~~The~~ sponsor states that "in 39 patients treated with pantoprazole for 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after four years".

In this NDA, the sponsor submits 53 studies evaluating the pharmacokinetics of pantoprazole following oral and intravenous administration. The intravenous pharmacokinetic studies allowed for a complete pharmacokinetic characterization of this NME. Pantoprazole and its metabolites were quantified by in studies evaluating unlabeled pantoprazole and by counting on a in studies evaluating ^{14}C-labeled pantoprazole. All analytical methods were adequately validated. All concentration values used for characterizing the kinetics of pantoprazole and its metabolites were $\geq$ the limit of quantification. Synthetic metabolites of pantoprazole were generally not available; subsequently, the metabolites were semiquantitatively evaluated (as mg equivalents of the parent drug).

Pantoprazole is metabolized mainly by CYP2C19, and to minor extents by CYPs 3A4, 2C9, 2D6. Its major metabolite is designated as M2 and the other four metabolites are designated as M1, M3, M4 and MX. CYP2C19 exhibits a genetic polymorphism, subsequently, individuals deficient in this isozyme are poor metabolizers of pantoprazole. Pantoprazole is a racemic compound with the center of activity at the sulfur atom. The genetic polymorphism of CYP2C19 is stereo-specific and affects mainly the metabolism of the (+)-enantiomer. The (-)-enantiomer is relatively more toxic than the (+)-enantiomer, however, selective development of the (+)-enantiomer is not recommended since it readily converts to the (-)-enantiomer.

Following oral or intravenous administration, pantoprazole distributes mainly in the extracellular fluid and is 98% bound to serum proteins (mainly albumin). It is rapidly cleared from the serum with a terminal elimination half-life of approximately 1.0 h. Since pantoprazole inhibits the proton pump non-competitively, the inhibition lasts a long time, subsequently, its dosing interval is 24 h. Thus, the dosing interval of pantoprazole is not related to, and cannot be predicted by, its serum half life. Due to the long dosing interval, pantoprazole accumulation does not occur in normal (extensive) metabolizers on multiple dose treatment regimens. Oral or intravenous doses of pantoprazole are eliminated mainly as its metabolites, 71% in urine and 18% in feces. No unmetabolized pantoprazole is eliminated in urine. Orally administered pantoprazole undergoes limited pre-systemic elimination ($\leq$ 15% of the dose).

The absolute bioavailability of the enteric coated 40 mg pantoprazole tablet is 77%. The pantoprazole formulation used in the Phase III clinical studies and the to-be-marketed formulation were similar in composition except for differences in spray patterns of the enteric coating material. These differences were due to the use of a larger scale equipment for the production of the to-be-marketed formulation. The Phase III clinical study enteric coated 40 mg tablet and the to-be-marketd enteric coated 40 mg tablet were bioequivalent. The 20 mg enteric coated tablets (dose =40 mg) used for the later part of the Phase II clinical development and the Phase III clinical study enteric coated 40 mg tablet were also bioequivalent. Pantoprazole dosage adjustment has been recommended for patients with severe hepatic impairment but is not necessary in patients with mild or moderate hepatic impairment, renally impaired patients and elderly patients. Pantoprazole exhibits no gender differences in kinetics and has not been evaluated in pediatric subjects. Food delays the onset of pantoprazole absorption and would, subsequently, delay the onset of its effect. However, overall drug exposure is not affected by food. Clinically relevant interactions of pantoprazole with drugs metabolized CYPs 2C19, 3A4, 2C9 and 2D6 do not occur. Antacids do not affect the absorption of pantoprazole. The slight increases noted in the peak serum concentration and overall exposure of digoxin upon co-administration with pantoprazole are brought to the attention of the sponsor as covered under Labeling Comment 9(b)(iii).

From a pharmacokinetic perspective, the NDA is considered approvable.

II. SUMMARY OF INFORMATION ON . PHARMACOKINETICS, BIOAVAILABILITY, BIOEQUIVALENCE, PHARMACODYNAMICS, ETC.

1. PHARMACOKINETICS:

(a) Intravenous Kinetics of Pantoprazole from Administration of Injection Concentrate Formulation: The pharmacokinetics of pantoprazole was characterized in 12 healthy male subjects receiving single pantoprazole doses of 10, 20, 40 and 80 mg in a cross over fashion by intravenous infusion over 15 min (Byk Gulden Protocol #FHP003; GMR-3007). Plots of mean ± SD serum concentration versus time for each dose level is presented in Fig. 1. The mean±SD pharmacokinetic parameters of pantoprazole obtained in this study are presented in Table 1.

Fig. 1. Mean ± SD Pantoprazole Serum Concentration Versus Time Following Single Intravenous Doses of 10, 20, 40 and 80 mg in 12 Normal Subjects

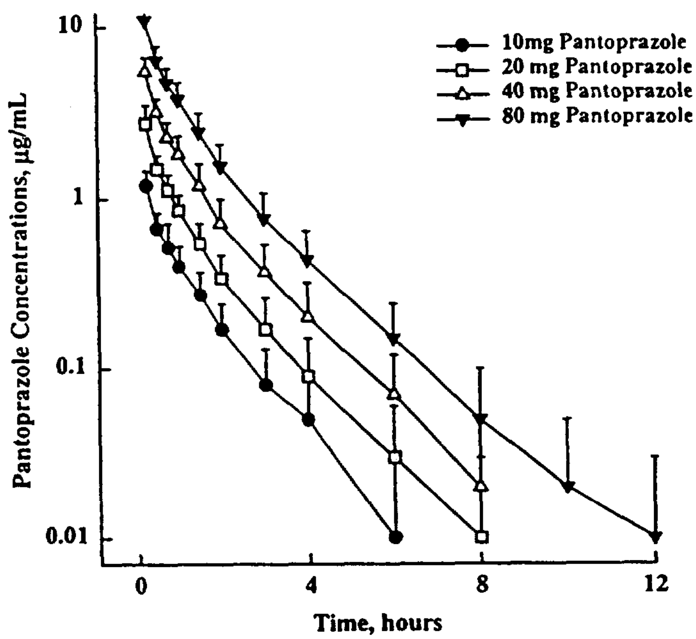


Table 1. Mean + SD Pantoprazole Pharmacokinetic Parameters and Standard Deviation Following Administration of 10, 20, 30 and 40 mg doses by Intravenous Infusion

Dose (mg)	n	C_{max} (mg/L)	t_{max} (h)	AUC ([mg/L]h)	$t_{1/2}$ (h)	Cl_T (L/h)	V_d (L)
10	12	1.19±0.26	0.25	1.2±0.4	0.9±0.2	9.0±2.9	11.7±3.1
20	12	2.74±0.75	0.25	2.6±0.8	1.1±0.4	8.3±2.9	11.5±3.1
40	12	5.52±1.42	0.25	5.4± 1.5	1.0±0.3	7.8±2.7	11.0±1.7
80	12	10.98±2.02	0.25	11.2± 3.0	1.2±0.3	7.6±2.2	12.0±2.1

AUC and pantoprazole concentration at end of the 15 min infusion (C_{max}) increased linearly with increasing dose (see Fig. 2).

Fig. 2. Assessment of Dose Linearity of AUC Following Intravenous Doses of 10, 20, 40 and 80 mg

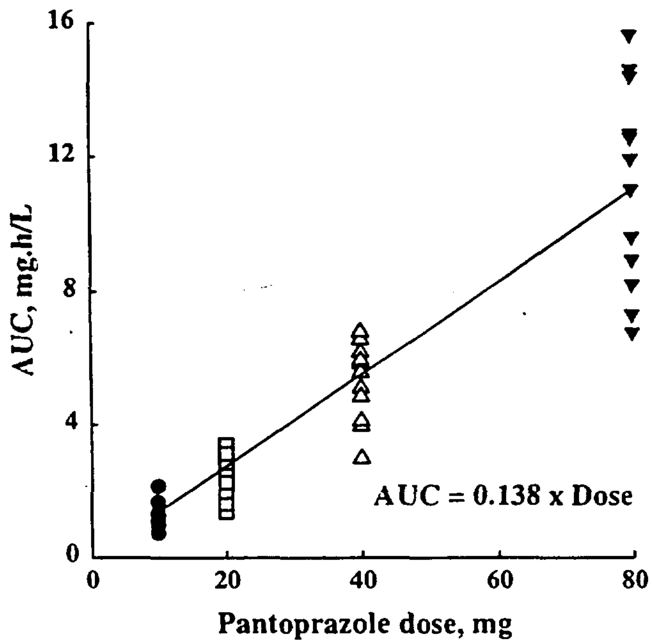


Table 2. ANOVA Assessment of Equivalence of Pantoprazole Pharmacokinetic Parameters Following Intravenous Doses of 10, 20, 40 and 80 mg with the 80 mg Dose as Reference

point estimates and 90%-confidence limits, reference: 80 mg

	Dose		
	10 mg	20 mg	40 mg
C(0.25 h)	0.91 (0.81, 1.03)	1.04 (0.92, 1.17)	1.06 (0.94, 1.20)
AUC(0-Inf)	0.85 (0.78, 0.92)	0.93 (0.85, 1.01)	0.97 (0.89, 1.06)

	Dose		
	10 mg	20 mg	40 mg
t½	0.80 (0.71, 0.91)	0.89 (0.79, 1.01)	0.90 (0.80, 1.02)
Cl/kg	1.18 (1.08, 1.28)	1.08 (0.99, 1.17)	1.03 (0.94, 1.12)
Vdarea	0.95 (0.83, 1.08)	0.94 (0.83, 1.07)	0.91 (0.80, 1.04)

The kinetics of pantoprazole was best described by the two-compartmental model. Across dose levels, the mean Cl_T, V_d and $t_{1/2}$ were, respectively, 7.6-9.0 L/h, 11.0-12.0 L and 0.9-1.2 h and were dose independent. The inter-compartmental rate constants and the volume of distribution in the central compartment were determined by simultaneously fitting the function (Q_t/V_c) describing the pantoprazole concentration versus time for the 20, 40 and 80 mg dose groups using a two-compartmental, first order elimination intravenous infusion model. Q_t and V_c represent the amount of pantoprazole in the central compartmental and apparent volume of distribution in the central compartment, respectively. The mean values of K_{12}, K_{21}, and K_{10} were 0.40 h^{-1}, 0.91 h^{-1} and 1.12 h^{-1}, respectively. The mean V_c was 6.9 L.

Using individual subject dose normalized, log transformed values, equivalence of the C_{max} (serum concentration at the end of infusion) and AUC of for the dose range (10-80 mg was assessed using ANOVA for the 90% confidence limits, with the 80 mg dose as reference and the 10, 20 and 40 mg doses tests, (Table 2). The point estimates and confidence intervals for C_{max} for the 10, 20 and 40 mg doses were entirely within the range of 0.80-1.25 required for equivalence as were those for AUC for the 20 and 40 mg doses. The lower 90% confidence limit for AUC of the 10 mg dose was 78%. Overall, it could be considered that dose proportional of AUC was established in the dose range of 10-80 mg for Cmax and AUC. Similarly, equivalence of body weight normalized Cl_T and V_d was established for the dose range of 10-80 mg indicating that these parameters are dose independent in this dose range.

The pharmacokinetics of pantoprazole was also evaluated in 6 male subjects each receiving a single 40 mg dose of ^{14}C-labeled pantoprazole (37.5 uCi) by constant rate intravenous infusion over 15 min (Byk GuldenProtocol #FHP108E). The mean values of body weight normalized Cl_T and Vd_{area} (0.123 L/h/kg and 0.152 L/kg, respectively) determined in this study, were within the range of values for the dose range in Table 2 which, when expressed per kg, are as follows: Cl_T ______ L/h/kg and Vd_{area}: ______ L/kg. The elimination half-life obtained in this study (0.89 h) also approximated 1 h. These findings suggest consistency of pharmacokinetic data across studies.

(b) Intravenous Kinetics of Pantoprazole from Injection Concentrate and Lyophile Formulations: The kinetics of pantoprazole was evaluated in 12 normal, male subjects each receiving a single 40 mg dose as an injection concentrate and 45.5 mg and 91 mg doses as a lyophile formulation. Each dose was administered by a 15 min constant rate intravenous infusion in a placebo controlled crossover study (Byk Gulden Protocol FHP027E; GMR-29734). The lyophile formulation is proposed for marketing for intravenous administration. The concentrate formulation was used for intravenous administration in the early clinical development. Plots of pantoprazole serum concentration versus time for the tested doses are presented in Fig. 3. The mean±SD pharmacokinetic parameters are presented in Table 3. CO and LY in parentheses represent concentrate formulation and lyophile formulation, respectively.

Fig. 3. Mean $\pm$ SD Pantoprazole Serum Concentration Versus Time For Single Intravenous Doses of 40 and 80 mg as Lyophile Formulation and 40 mg as Injection Concentrate.

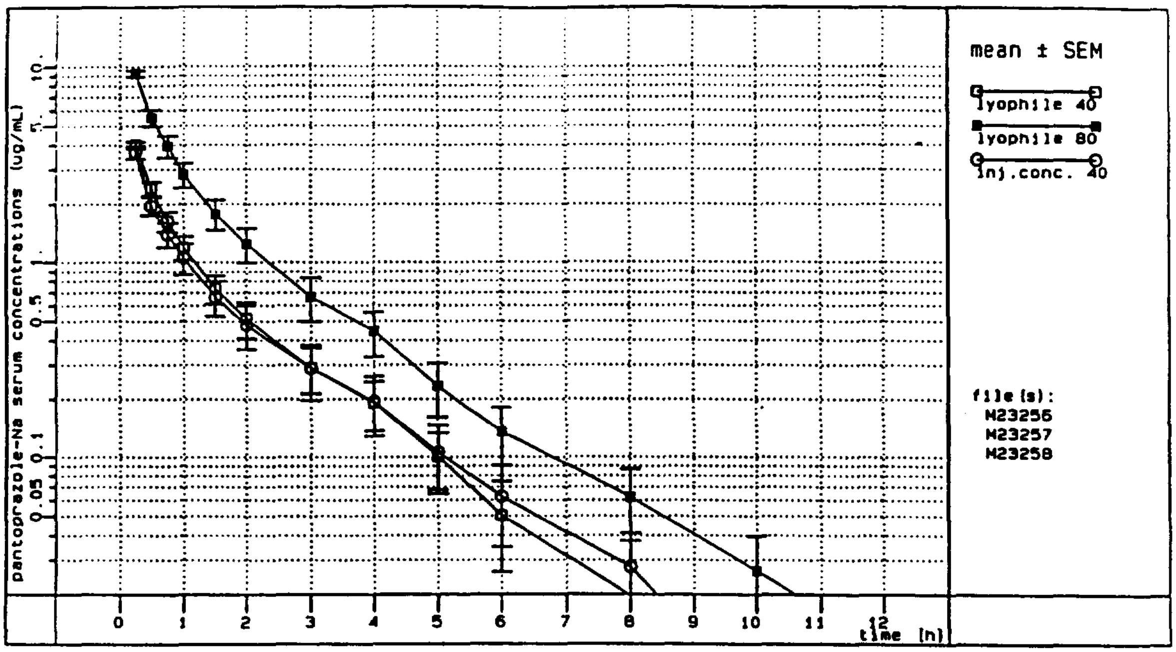


Table 3. Mean + SD Pantoprazole Pharmacokinetic Parameters in Normal Subjects Following Administration of 10, 20, 30 and 40 mg doses by Intravenous Infusion

Dose (mg)	n	C_{max} (mg/L)	t_{max} (h)	AUC ([mg/L]h)	$t_{1/2}$ (h)	Cl_T (L/h)	V_d (L)
40(CO)	12	3.67±0.95	0.25	3.6±2.2	1.3±0.3	14.0±6.4	23.6±8.8
45.5(LY)	12	4.00±0.55	0.25	4.0±1.9	1.2±0.3	11.7±4.0	19.3±6.3
91(LY)	12	9.24±1.15	0.25	9.3± 4.5	1.2±0.3	10.3±4.2	17.2±5.3

Panroprazole half-life values were similar for the three treatments as were the Cl_T and V_d values for the two lyophile formulation. Cl_T and V_d values for the injection concentrate appeared to be slightly greater than those for the two lyophile formulations. C_{max} values for the 40 mg lyophile injection and the 40 mg injection concentrate were similar. In this study, for the 40 mg dose of injection concentrate, both the mean Cl_T and V_d approximately 100% higher and the mean AUC was 50% lower as compared to values obtained in Byk Gulden Protocol FHP003 (see page 3). No explanation was provided as to the observed kinetic differences between the two intravenous formulations. Since the increases in Cl_T and V_d were similar, the half-life values for both studies (1.0-1.3 h) were similar.

The results of comparison of log transformed AUC by the Two One-sided T-tests Procedure for the 90% confidence limits for (i) the 40 mg injection concentrate dose as reference versus the 45.5 mg lyophile dose (adjusted to 40 mg) as test and (ii) the 40 mg lyophile dose as reference versus the 91 mg lyophile dose (adjusted to 80 mg) as test are presented in Table 4.

Table 4. Pantoprazole AUC Equivalence: 40 mg Lyophile Formulation Versus 40 mg Injection Concentrate and 40 mg Lyophile Formulation Versus 80 mg Lyophile Formulation

Two One-sided T-Tests	Test/Reference (%)	
	Point Estimate	90% Confidence Limits
Reference: 40 mg Inj. Conc. Test: 40 mg Lyophile	100	90 – 110
Reference: 40 mg Lyophile Test: 80 mg Lyophile (adjusted)	116	107 – 125

In both cases, the point estimates and the confidence of limits of the ratio (test/reference) of the mean log transformed AUC values were in the interval of 80-125%. These findings suggest (i) that the systemic exposures for the 40 mg pantoprazole injection concentrate, that was used for the early clinical development, and the 40 mg pantoprazole lyophile formulation that is proposed for marketing for intravenous administration, are equivalent and (ii) that the systemic exposure for 40 mg pantoprazole lyophile proposed for marketing for intravenous administration and 80 mg pantoprazole lyophile are dose proportional. However, dose proportionality is not an issue of concern as only the 40 mg dose is proposed for marketing.

(c) Oral Administration: Single Dose: The kinetics of pantoprazole for the orally administered enteric coated tablet was characterized for the dose range of 10-80 mg (Byk Gulden Protocol #A9907-GER; GMR 29717) in 10 normal male subjects. Plots of mean ± SD pantoprazole serum concentration versus time are presented in Fig. 4. The mean ± SD pantoprazole pharmacokinetic parameters are presented in Table 5. Also presented in Table 5 are the mean ± SD pharmacokinetic parameters for the 40 mg enteric coated tablet formulations used in the bioequivalence studies submitted in this NDA (Byk Gulden Protocols FHP028E, FHP014 and FHP041).

Fig. 4. Plots of Mean ± SD Pantoprazole Serum Concentration Versus Time Following Single Oral Doses of 10, 20, 40 and 80 mg in 12 Normal Subjects

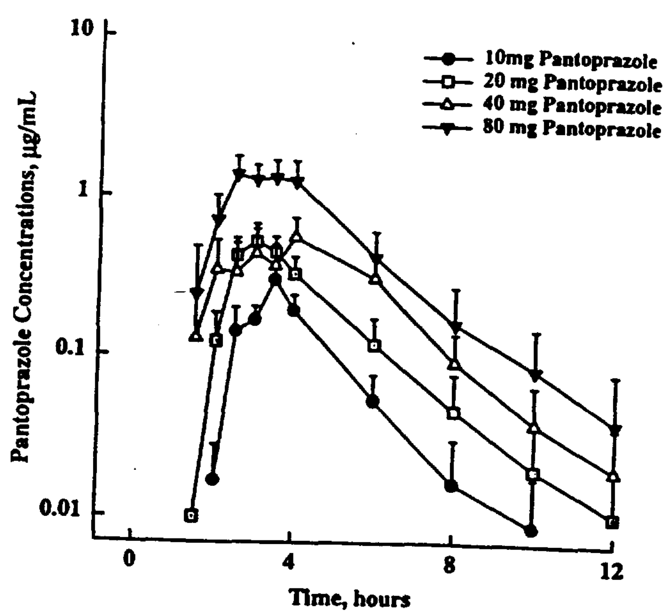


Table 5. Mean ± SD Pantoprazole Pharmacokinetic Parameters in Normal Subjects Following Administration of Single Oral Doses of 10, 20, 40 and 80 mg

Protocol	n	Dose (mg)	C_{max} (ug/mL)	t_{lag} (h)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)
A9907-GER	9	10[I]	0.41±0.12		3.1±0.5	0.7±0.6	0.9±0.6
GMR-2917	10	20[I]	0.78±0.37		3.2±1.1	1.5±1.4	0.9±0.6
	9	40[I]	1.20±0.56		3.7±1.5	2.6±1.6	1.2±0.7
	10	40[I*]	1.39±0.62		3.2±1.2	2.8±2.1	0.9±0.3
	10	80[I]	2.78±1.12		3.1±1.2	5.0±4.1	0.9±0.6
FHP014	35	40[IIa]	2.30±0.7	1.8±1.0	2.8±1.1	4.3±2.0	1.2±0.3
GMR-29687	1[pm]	40[IIa]	2.71	2.0	3.0	27.0	10.0
	35	40[III]	2.42±0.77	1.4±0.7	2.5±0.8	4.4±2.1	1.2±0.3
	1[pm]	40[III]	3.59	1.0	2.0	32.0	9.1
FHP028	35	40[III]	2.50±1.06	1.5±0.8	2.6±0.9	4.9+3.2	1.2±0.4
GMR-29716	1[pm]	40[III]	4.03			38.4	6.7
	35	40[mf]	2.45±0.77	1.4±0.6	2.4± 0.6	4.2±2.8	1.2±0.4
	1[pm]	40[mf]	4.36			34.0	8.4
FHP041	36	40[mf]	2.51±0.67	1.7±0.8	2.6±0.9	4.6±2.0	1.2±0.3
GMR-31756	36	40[nf]	2.58±0.84	1.4±0.8	2.5±1.1	5.1±2.4	1.3±0.4

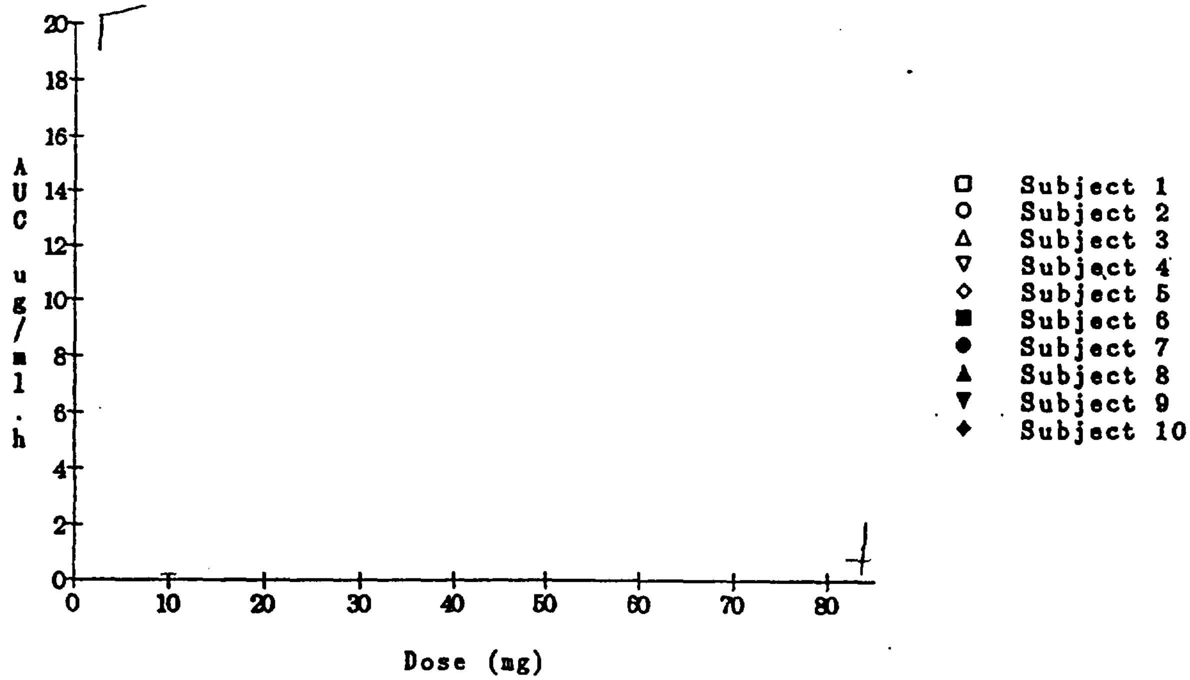
[I]Early Phase I Formulation (Formulation A), [*]Repeated; [II]Phase II formulation; [III]Phase III formulation, [mf]To-be-marketed formulation; [nf]New formulation, [pm]Poor metabolizer. [a]2 x20 mg tablet.

In extensive metabolizers of pantoprazole receiving the 40 mg dose, the pharmacokinetic parameters of pantoprazole were comparable across studies for the later formulations (Phase IIb, Phaes III, the to-be-marketed and the new enteric coated 40 mg pantoprazole tablet formulations). For this dose, the C_{max} and AUC obtained in the dose ranging study (Protocol A9907-GER) were markedly lower than the values for the Phase IIb, Phase III and the to-be-marketed formulations. This could be due to differences between the formulation used in the initial stages of drug development versus the improved, later phase and to-be-marketed formulations. Across studies, t_{max} and $t_{1/2}$ were dose independent.

In the dose ranging study (Protocol A9907-GER; GMR-2917), AUC and Cmax were dose linear in the dose range of 10-80 mg (Fig.5). Generally, dose normalized AUC values were equivalent (Fig. 6a) suggesting its dose proportionality in this dose range except that one subject showed significant deviation from dose proportionality. Dose normalized C_{max} values were not equivalent (Fig. 6b), subsequently, C_{max} was not considered dose proportional in this dose range. However, dose proportionality is not an issue of concern as only the 40 mg dose is proposed for marketing.

Fig. 5. Assessment of Dose Linearity of AUC (a) and C_{max} (b) Following Oral Pantoprazole Doses of 10, 20, 40 and 80 mg

(a)



(b)

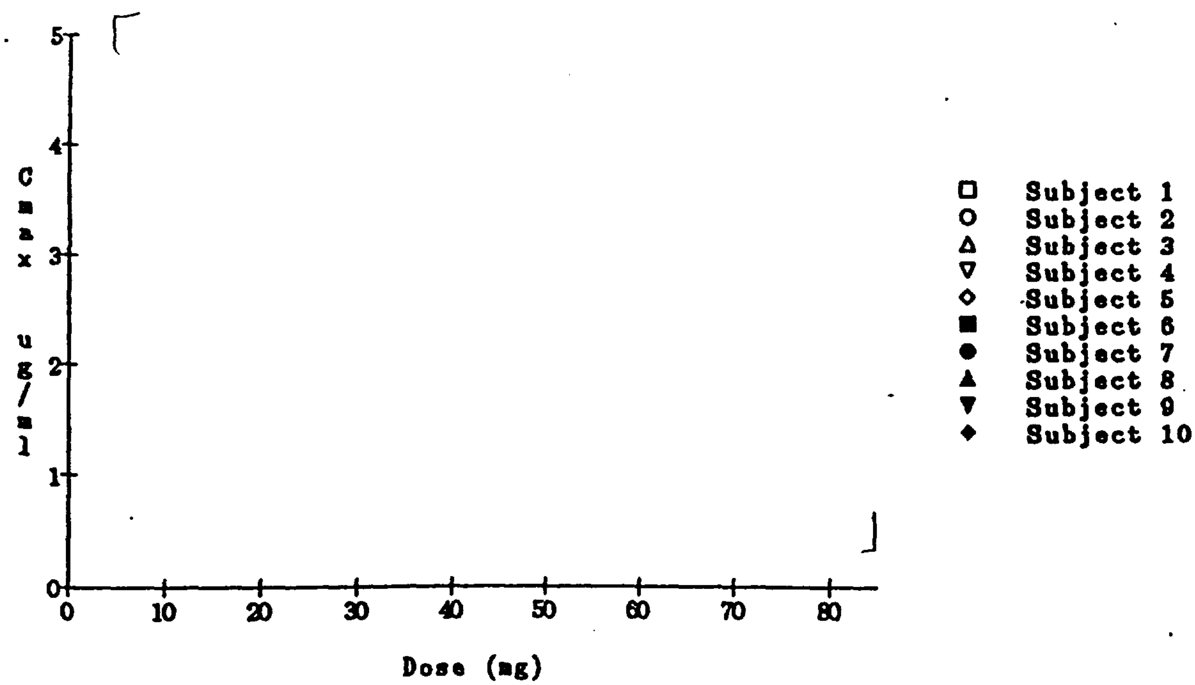
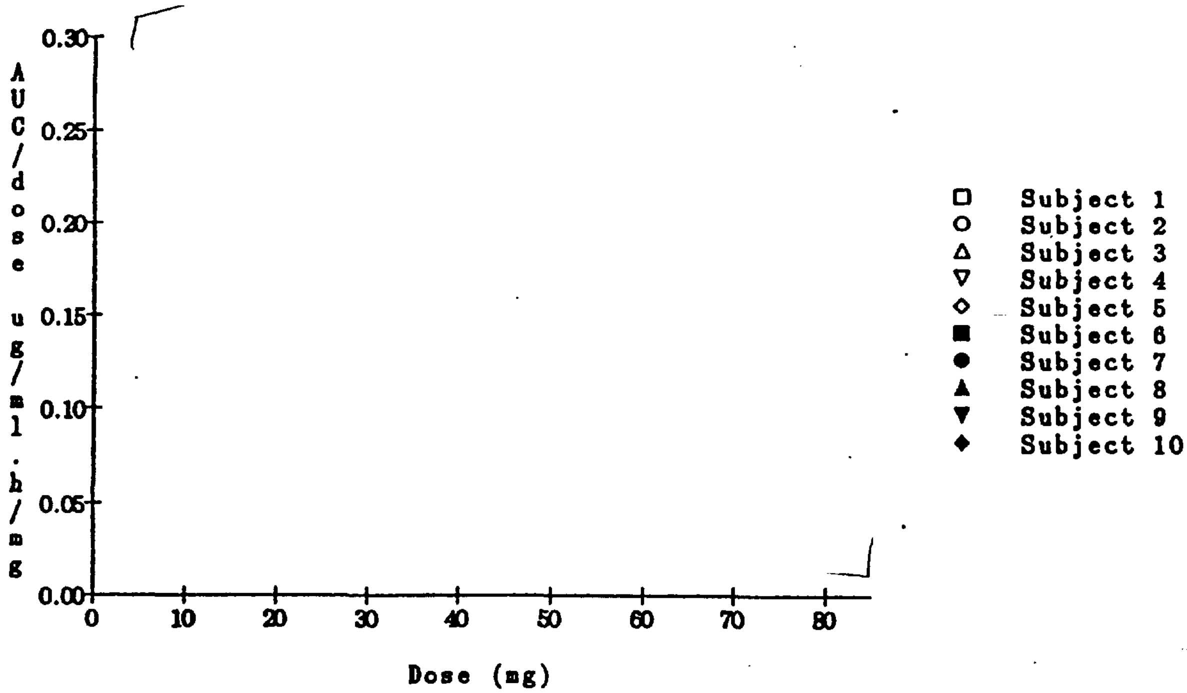
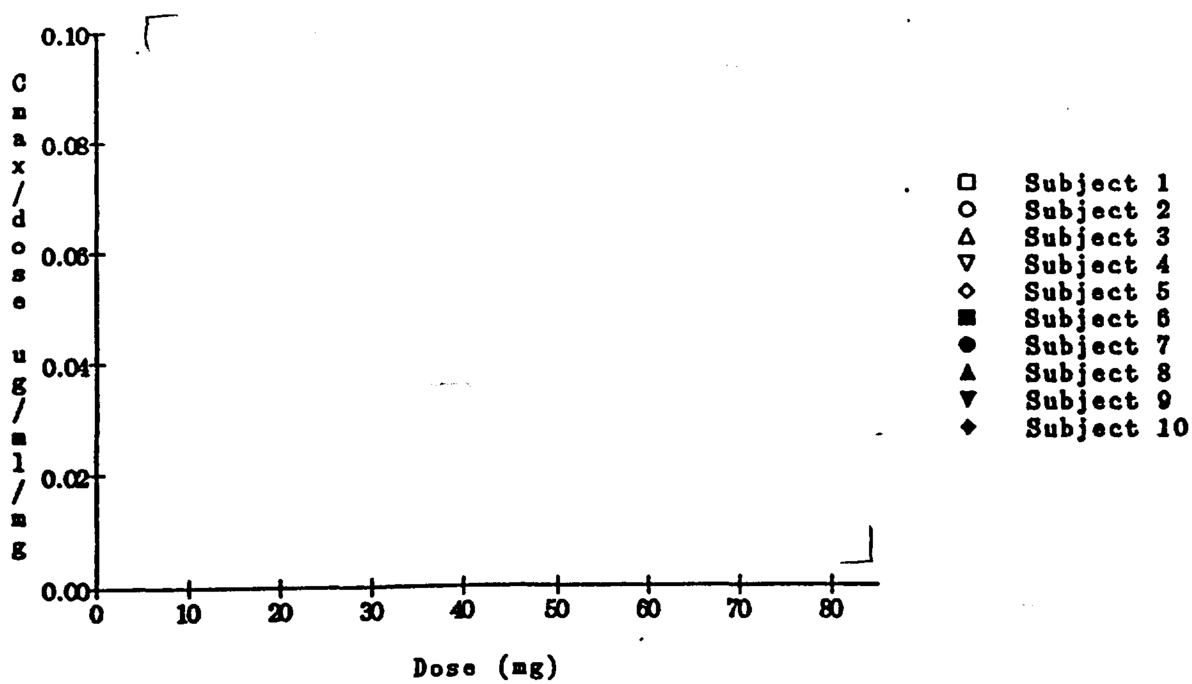


Fig. 6. Relationship between Dose normalized AUC (a) and C_{max} (b) Following Oral Pantoprazole Doses of 10, 20, 40 and 80 mg

(a)



(b)



(d) Oral Administration: Multiple Dose: The multiple dose kinetics of orally administered enteric coated pantoprazole tablet was determined in 16 healthy male subjects receiving the 20, 40 and 80 mg doses for 7 days (Byk Gulden Protocol #FK3029; GMR-29707) and in 12 healthy male subjects receiving the 20 and 40 mg doses also for 7 days (Byk Gulden Protocol #FHP007E; GMR-30133). In each study, the doses were administered in a crossover fashion. Plots of mean ± SEM pantoprazole serum concentration versus time for Byk Gulden Protocol FHP007E are presented in Fig. 7. The mean ± SD pharmacokinetic parameters of pantoprazole for both studies are provided in Table 6.

Fig. 7. Plots of Mean ± SD Pantoprazole Serum Concentration Versus Time for Days 1 and 7 Following Multiple Oral Doses of 20 and 40 mg in 12 Normal Subjects

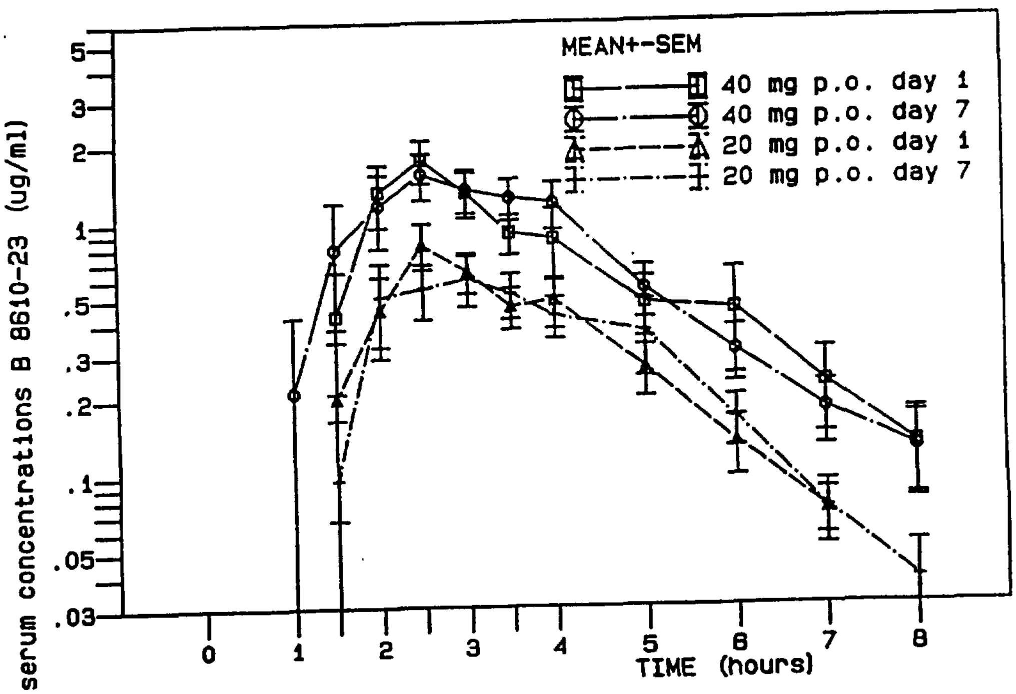


Table 6. Mean + SD Pantoprazole Pharmacokinetic Parameters in Normal Subjects Following Multiple Oral Doses of 20 and 40 mg

Protocol	n	Day	Dose (mg)	C_{max} (ug/mL)	tlag (h)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)
FR3029	15	7	20	1.02±0.30	—	2.1±1.4	1.7±0.6	1.2±0.2
GMR-29707	1 [redacted]	7	20	1.54	—	2.43	12.8	6.1
	15	7	40	2.16±0.85	—	1.9±0.5	3.2±1.1	1.0±0.2
	1 [redacted]	7	40	3.80	—	2.43	26.2	5.8
	15	7	80	4.08±1.25	—	1.9±10.6	7.2±2.8	1.3±0.6
	1 [redacted]	7	80	5.91	—	2.43	50.7	5.6
FHP007E	11	1	20	1.19±0.31	—	2.7±0.7	2.2±0.8	1.1±0.3
GMR-30133	12	7	20	1.23±0.30	—	3.0±0.9	2.1±0.6	1.0±0.5
	12	1	40	2.61±0.76	—	2.8±1.2	4.9+1.9	1.1±0.5
	11	7	40	2.52±0.77	—	2.5± 0.9	4.7±1.1	1.1±0.5

The multiple dose pharmcokinetic parameters of orally administered enteric coated pantoprazole tablets were similar to its single dose values for the 20 and 40 mg tablets (Byk Gulden Protocol FHP007E). T_{max} and $t_{1/2}$ were dose independent in both studies. In extensive metabolizers, $t_{1/2}$ values for both studies were similar. For the 40 mg dose, the mean C_{max} values for Protocol FHP007E were slightly (17-21%) higher. The mean AUC for this study (Protocol FHP007E) was 47-53% higher.

(e) Systemic Accumulation in Normal Metabolizers upon Multiple Oral Dosing: The results of Byk Gulden Protocol FHP007E in Table 7 above show that in extensive metabolizers, pantoprazole C_{max} for Day 1 and Day 7 were similar. These results suggest that in normal, metabolizers (all subjects in this study were normal metabolizers), pantoprazole would not accumulate in the serum upon multiple dosing.

(f) Systemic Accumulation in Poor Metabolizers upon Multiple Oral Dosing: In Byk Gulden Protocols FHP014 and FHP028, some poor metabolizers of pantoprazole, with dramatically high AUC and $t_{1/2}$ values, were identified (see Table 5). It was noted that the C_{max} values for these poor metabolizers were not equally dramatically higher than those of the normal metabolizers. Steady state C_{max} values were not determined since these were single dose studies. This reviewer has, therefore, predicted the potential of steady state accumulation of pantoprazole in poor metabolizers using the following standard pharmacokinetic equation:

$$R = 1/(1-e^{-K\tau})$$

where R is the accumulation ratio (factor), K is the terminal elimination rate constant and τ is the dosing interval for pantoprazole (24 h). The worst case scenario is the subject with the half-life of 10 h. In this subject, the accumulation ratio is only 1.23 (i.e., the ratio, $C_{max[ss]} : C_{max[dose\ \#1]}$ would be 1.23: 1.00). This finding suggests that even in poor metabolizers with pantoprazole half-life as long as 10 h (half-life is approximately 1 h in extensive metabolizers), there would be no significant steady state drug accumulation upon multiple dosing. This is due to the long dosing interval (24 h) of the drug.

2. BIOAVAILABILITY: The absolute bioavailability of pantoprazole enteric coated tablet was studied in 12 healthy male subjects each receiving a single oral dose of 40 mg (2x20 mg tablets) and a single 40 mg dose by intravenous infusion over 15 min in a crossover fashion (Byk Gulden Protocol #A9915-GER; GMR-29728). The mean absolute bioavailability (AUC_{oral}/AUC_{IV}) was 77% (range=______%). Excluding the single poor pantoprazole metabolizer ($t_{1/2}$>3.5 h for both routes of administration) did not significantly affect the mean absolute bioavailability (76% in this case).

3. BIOEQUIVALENCE:

(a) **Bioequivalence of the To-be-marketed Formulation and the Phase III Clinical Safety and Efficacy Study Formulation:** The bioequivalence of the to-be-marketed enteric coated 40 mg pantoprazole tablet formulation (Formulation E: test) and the enteric coated 40 mg tablet that was used in the Phase III clinical safety and efficacy trials (Formulation C: reference) was assessed in 36 healthy male subjects (Byk Gulden Protocol #FHP028E). Plots of the mean + SEM serum concentration of pantoprazole versus time for both formulations are presented in Fig. 8. The mean + SD of all pharmacokinetic parameters have already been presented (see Table 5).

Fig. 8. Plots of Mean ± SEM Pantoprazole Serum Concentration Versus Time Following a Single Oral Dose 40 mg of Phase III Clinical Study Formulation or the Proposed Market Formulation in 36 Normal Subjects

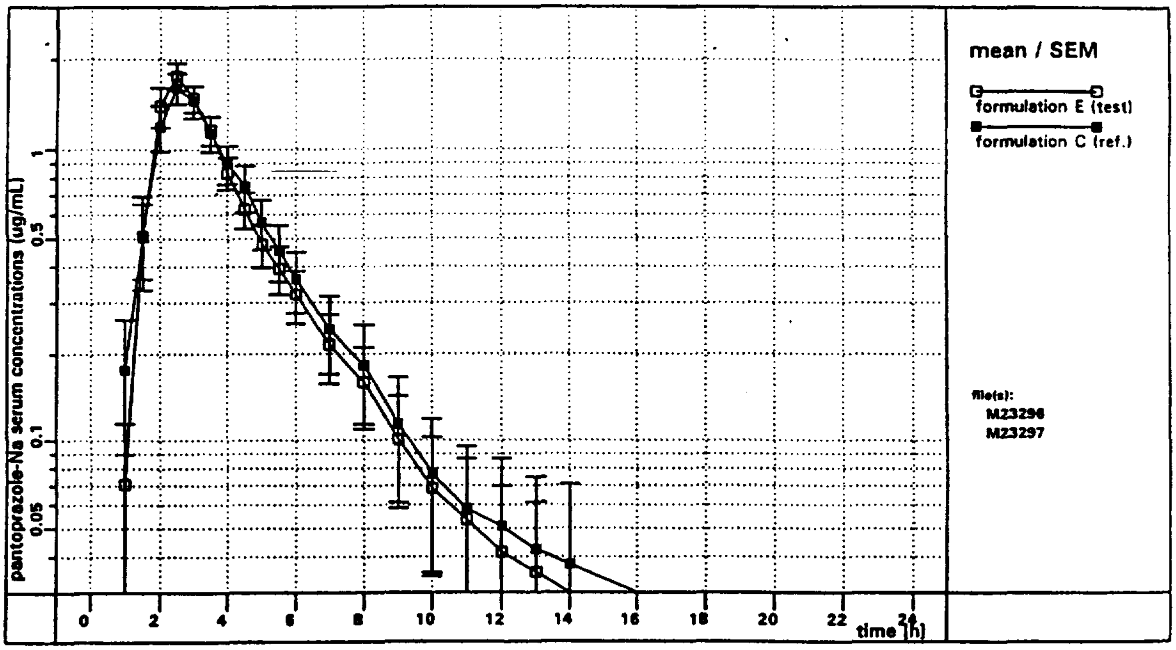


Table 7. Assessment of Bioequivalence Phase III clinically Tested Formulation and the Proposed Market Formulation

Pantoprazole 40 mg p.o. Pharmacokinetic characteristic	Reference: formulation C		Test: formulation E		Equivalence ratio (Test/Reference) Point estimate	90%-confidence interval after logarithmic transf.$)	
	Geometric mean, n = 36 exp (mean(ln) ± SD (ln)) $)						
AUC(0,Inf.)(μg/mLxh)	4.37	(2.25, 8.47)	4.35	(2.21, 8.56)	1.00	0.92	1.07
Cmax (μg/mL)	2.28	(1.41, 3.68)	2.32	(1.65, 3.27)	1.02	0.91	1.15
t1/2 (h)	1.17	(0.77, 1.79)	1.23	(0.76, 1.98)	1.05	1.00	1.11
tmax-tlag (h)	1.19	(0.74)	1.00	(0.34)	-0.19	-0.43	+0.04

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

The bioequivalence of the the test formulation (Formulation E) and the reference formulation (Formulation C) was assessed using the Two One-sided Test Procedure for the 90% confidence limits. The ratios (test/reference) of the mean values of log transformed C_{max} and AUC were within the interval of 0.80-1.25 required for bioequivalence (Table 7). Therefore, the bioequivalence of the to-be-marketed enteric coated 40 mg pantoprazole tablet and the enteric coated 40 mg tablet that was used in the Phase III clinical safety and efficacy studies has been demonstrated.

(b) Bioequivalence of Two 20 mg Enteric Coated Phase IIb Tested Pantoprazole Tablets (Formulation B: test) and One Phase III Tested 40 mg Enteric Coated Tablet (Formulation C: reference): The bioequivalence of the 2x20 mg enteric coated tablets that were used in the Phase IIb clinical safety and efficacy trials (Formulation B:test) and the 1x40 mg enteric coated pantoprazole tablet that was used in the Phase III clinical safety and efficacy trials (Formulation C: reference) was assessed in 36 healthy male subjects (Byk Gulden Protocol #FHP014; GMR-29687). The mean plots of mean serum concentration of pantoprazole versus time for these formulations were not provided; therefore typical individual subject plots are presented in Fig. 9. The mean + SD pharmacokinetic parameters for this study have already been presented (see Table 5).

Fig. 9. Typical Plots of Individual Subject Pantoprazole Serum Concentration Versus Time Following a Single Oral Dose 40 mg of Phase III Clinical Study Formulation or the 2 x 20 mg Phase IIb Formulation in 36 Normal Subjects

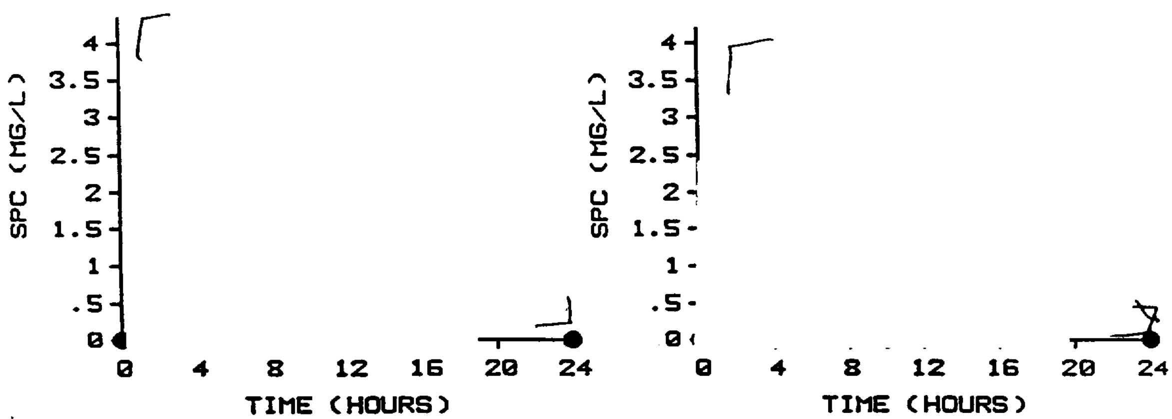


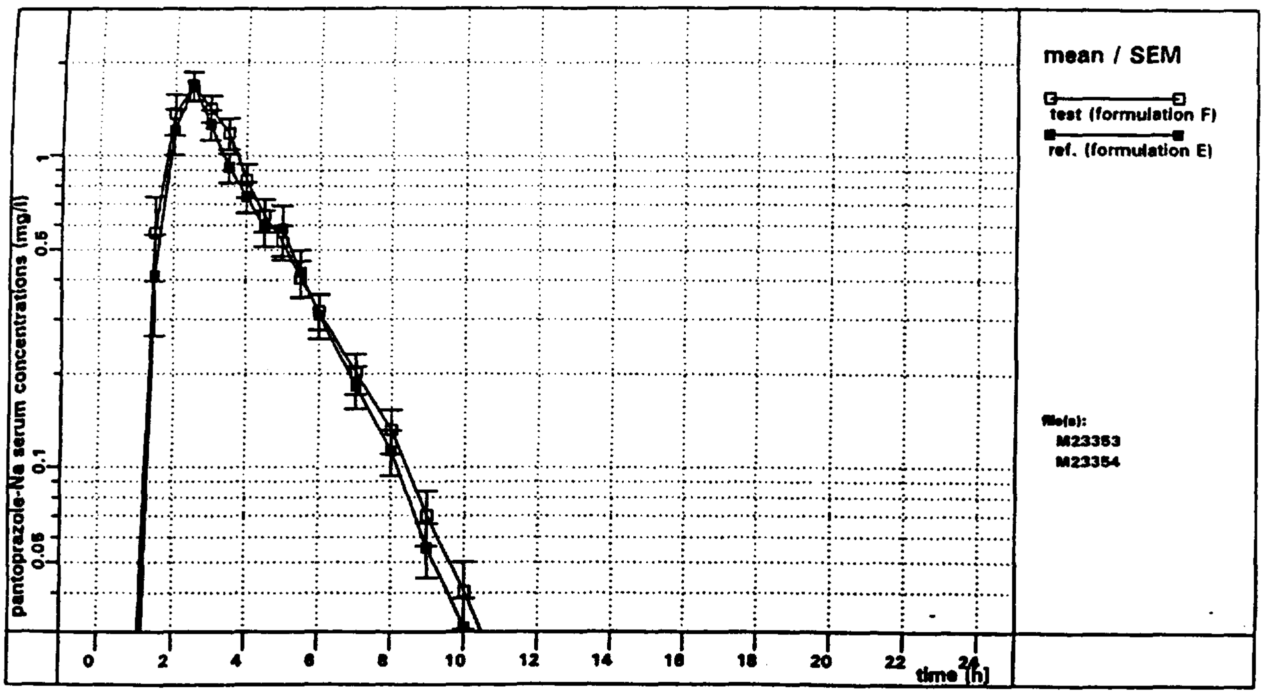
Table 8. Assessment of Bioequivalence Phase III clinically Tested Formulation and the Phase IIb Clinically Study Formulation

Pantoprazole a single oral dose of 40 mg in each period Pharmacokinetic Characteristic	Reference: 40 mg tablet (Phase III form.)	Test: 2 x 20 mg tablets in a capsule (Phase IIb form.)	Bioequivalence ratio (Test/Reference) Point estimate	90%-confidence interval after logarithmic transformation
	Geometric mean, n = 36 (exp(mean(ln) ± sd(ln))			
AUC(0,oo) (mg/l h)	4.22 (2.43, 7.32)	4.14 (2.44, 7.04)	0.98	0.94, 1.02
Cmax (mg/l)	2.31 (1.70, 3.15)	2.20 (1.65, 2.94)	0.95	0.89, 1.01
Half-life (h)	1.28 (0.85, 1.92)	1.27 (0.82, 1.96)	0.99	0.96, 1.03

The bioequivalence of the test formulation (Formulation B) and the reference formulation (Formulation C) was assessed using the Two One-sided Test Procedure for the 90% confidence limits. The ratios (test/reference) of the mean log transformed Cmax and AUC were within the interval of 0.80-1.25 that is required for bioequivalence (Table 8). Therefore, the bioequivalence of the Phase IIb 2x20 mg enteric coated pantoprazole tablets and the 40 mg enteric coated pantoprazole that was used in the Phase III clinical safety and efficacy studies has been demonstrated.

(c) Bioequivalence of a New Formulation and the To-be-marketed Formulation: The bioequivalence of new enteric coated 40 mg pantoprazole tablet formulation (Formulation F: test) and the to-be-marketed enteric coated 40 mg pantoprazole tablet formulation (Formulation E: reference) was assessed in 36 healthy male subjects (Byk Gulden Protocol #FHP041, GMR-31756). Plots of the mean ± SEM plots of serum concentration of pantoprazole versus time for both formulations are presented in Fig.10. The mean ± SD pharmacokinetic parameters for this study have already been presented (see Table 5).

Fig. 10. Plots of Mean ± SEM Pantoprazole Serum Concentration Versus Time Following a Single Oral Dose 40 mg of a Enteric Formulation or the Proposed Enteric Coated Market Formulation in 36 Normal Subjects



The bioequivalence of the test formulation (Formulation F) and the reference formulation (Formulation E) was assessed using the Two One-sided Test Procedure for the 90% confidence limits. The ratios (test/reference) of the mean log transformed AUC and Cmax were within the interval of 0.80-1.25 that is required for bioequivalence (Table 9).

Table 9. Assessment of Bioequivalence Phase III Clinical Study Formulation and the Phase IIb Clinical Study Formulation

Pharmacokinetic characteristic of pantoprazole-Na	**Reference:** geometric mean (N=36) (68%-range)	**Test:** geometric mean (N=36) (68%-range)	**Equivalence ratio (Test/Reference) Point estimate (90% confidence interval)**
AUC (mgxh/l)	**4.11** [redacted]	**4.51**	**1.10 (1.03, 1.16)**
C_{max}/AUC (1/h)	**0.577** [redacted]	**0.516** [redacted]	**0.89 (0.83, 0.96)**
$t_{1/2}$ (h)	**1.18**	**1.26** [redacted]	**1.07 (1.02, 1.12)**
C_{max} (mg/l)	**2.37** [redacted]	**2.33** [redacted]	**0.98 (0.90, 1.07)**

The ratio (test/reference) of the mean values of log transformed Cmax/AUC, which the sponsor also used as an indicator of bioequivalence was within the interval of 0.80-1.25. Therefore, the bioequivalence of the new enteric coated 40 mg pantoprazole tablet formulation (Formulation F) and the to-be-marketed enteric coated 40 mg pantoprazole tablet formulation (Formulation E) has been demonstrated.

4. METABOLISM:

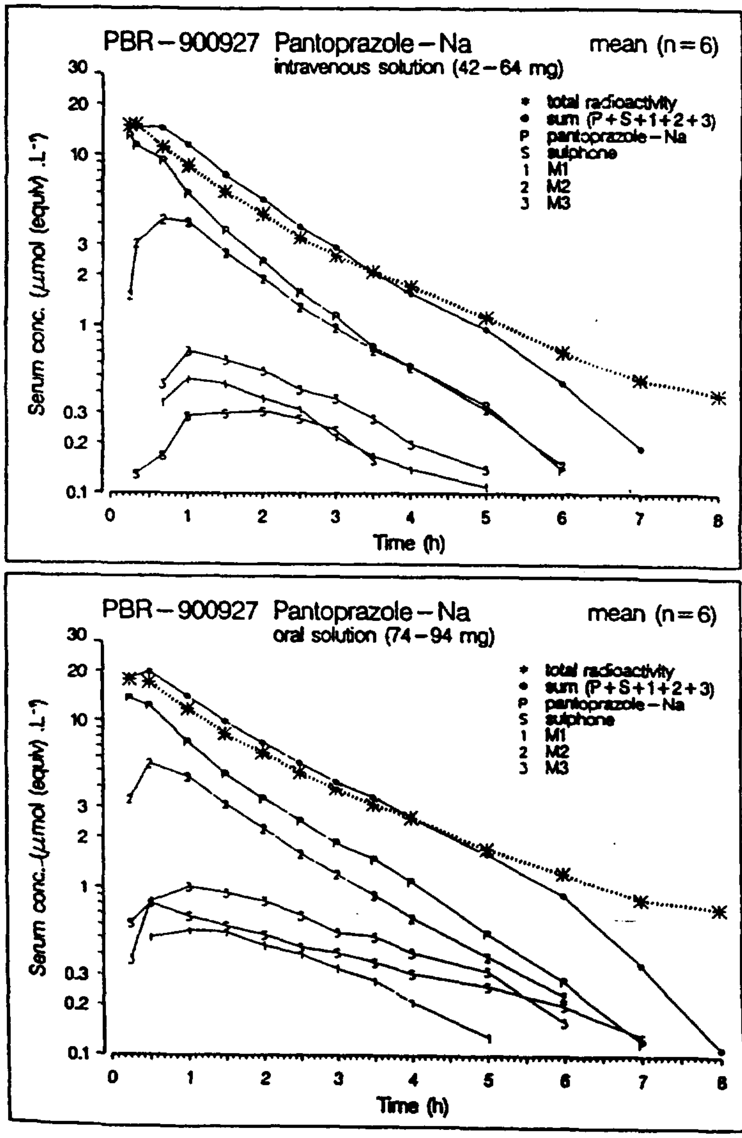
(a) **Metabolic Pathways**: The metabolism of pantoprazole was evaluated in 6 healthy male volunteers who received a single 60 mg dose of the ^{14}C-labeled drug (37.5 uCi) as an intravenous injection over 15 min and a single 80 mg dose of the labeled drug (50 uCi) as an oral solution in a crossover fashion (Byk Gudlden Protocol #FHP018E, GMR-29693). The main pathways of pantoprazole. metabolism are presented in Fig. 11.

Fig. 11. Pathways of Pantoprazole Metabolism

Three primary metabolic pathways were identified: (a) demethylation by CYP2C19 with subsequent sulfate conjugation to a p-O-desmethyl-O-sulfate derivative designated as M2, (b) oxidation by CYP3A4 to a sulfone and (c) reduction at the sulfur atom and demethylation to a p-O-desmethyl-sulfide derivative designated as M3-deconjugate, a portion of which undergoes sulfate conjugation to a p-O-desmethyl-O-sulfate sulfide derivative designated as M3, as well as glucuronic acid conjugation to a p-O-desmethyl-O-glucuronyl sulphide derivative designated as M4. M2 is further oxidized by CYP3A4 to a p-O-desmethyl-O-sulfate sulphone derivative designated as M1. The sulfone metabolite is demethylated by CYP2C19 with subsequent sulfate conjugation also to M1. The sponsor states that CYP2C9 and CYP2D do play minor roles in pantoprazole metabolism. However, the metabolic pathways mediated by these two isozymes have not been specified.

An unidentified metabolite, designated as MX, was also formed from pantoprazole. In this study, the sulfone metabolite was not detected in urine whereas M4 and MX were not detected in serum. Plots of the serum concentration of pantoprazole and its main metabolites are presented in Fig. 12.

Fig 12. Plots of Mean Serum Concentrations of Total Radioactivity, Pantoprazole and its Metabolites Following Administration of ^{14}C-labeled Pantoprazole as an Intravenous Injection (60 mg) and as an Oral Solution (80 mg) in Six Normal Subjects



The serum concentrations of pantoprazole metabolites were in the order of M2> >M3 (in all forms)> M1 >sulfone following intravenous infusion and M2> >M3 (in all forms) >sulfone>M1 following oral solution administration .

Pantoprazole was eliminated mainly in urine, as its metabolites, and to a minor extent in feces. No unmetabolized pantoprazole was excreted in urine The mean cumulative percentages of the administered doses ultimately eliminated in urine and feces, were, respectively, 70.9% and 18.5% for the intravenous dose and 72.4% and 18.45% for the dose of oral solution (Table 10).

Table 10. Renal and Fecal Excretion of Total Radioactivity Following Administration of ^{14}C-labeled Pantoprazole as an Intravenous Solution (60 mg) and as an Oral Solution (80 mg) in Six Normal subjects

Characteristic		Mean	SD	Median	Range
A^e_{urine}	i.v.	70.9	7.6	68.7	
(% of actual dose)	oral	72.4	6.4	74.8	
A^e_{faeces}	i.v.	18.5	4.8	19.2	
(% of actual dose)	oral	18.4	6.3	15.0	
A^e_{total}	i.v.	89.4	5.1	91.2	
(% of actual dose)	oral	90.7	1.4	90.8	

The mean cumulative renal excretion was 29.3% of the intravenous dose versus 37.7% of the oral dose at 8 h postdose and 37.9% for the intravenous dose versus 46.1% for the oral dose at 24 h postdose. The higher cumulative metabolite values for the oral route at 8 and 24 hours postdose is likely to be related to pre-systemic metabolism. At 24 h postdose pantoprazole metabolites ultimately excreted in urine were in the following order of M2> > M3-decongugate> M1> M4=MX > M3 for the intravenous dose and M2> > M3-deconjugate> M1> M4> MX> M3 for the oral dose. Based on these findings, M2 is the major metabolite of pantoprazole and CYP2C19 is the predominant isozyme for its metabolism. The roles of the other isozymes (CYPs 3A4, 2C9 and 2D6) are relatively minor.

CYP2C19 exhibits a genetic polymorphism and is deficient in some individuals (e.g., 3-5% of Caucasians and 15-20% of Indians). It is expected that some patients (those deficient in this isozyme) would be poor metabolizers of pantoprazole as compared to those with normal amounts of the isozyme (normal metabolizers) who would metabolize the drug more efficiently. This would result in pantoprazole kinetic differences between these two sub-populations.

In a study evaluating the kinetics of a 50:50, racemate of pantoprazole in poor metabolizers (n=4), the mean elimination half-lives of the unresolved pantoprazole and the (+)- and (-)- enantiomers, were 5.4 h, 8.0 h and 3.0 h, respectively (Byk Gulden Report 227/92; GMR-30131 [see Item 5 below]). Furthermore, 2-3 half-lives following dose administration, 80-90% of pantoprazole in the serum was in the form of the (+)-enantiomer in these subjects. These findings suggest that only the metabolism of the (+)- enantiomer of pantoprazole is significantly affected by the genetic polymorphism exhibited by CYP2C19.

(b) **Metabolite Kinetics**: The pharmacokinetic parameters of pantoprazole, M2 and the sum of pantoprazole and its serum metabolites following an intravenous dose of 60 mg and an oral dose of 80 mg in normal volunteers are presented in Table 11.

Table 11. Pharmacokinetic Parameters of Pantoprazole and Metabolites Following Administration of ^{14}C-labeled Pantoprazole as an Intravenous Solution (60 mg) and as an Oral Solution (80 mg) in Six Normal subjects

Characteristic		Mean	SD	Median	Range
		PANTOPRAZOLE			
c_{max} (μmol.L^{-1})	oral	14.25	1.50	13.88	
t_{max} (h)	oral			0.25	
AUC_{0-inf} (μmol.h.L^{-1})	i.v.	16.15	2.95	16.00	
	oral	20.96	8.05	17.00	
$t_{½}$ (h)	i.v.	0.89	0.25	0.88	
	oral	1.07	0.16	1.05	
Cl (L.h^{-1}.kg^{-1})	i.v.	0.123	0.021	0.119	
$V_{d_{area}}$ (L.kg^{-1})	i.v.	0.152	0.026	0.152	
		METABOLITE M2			
c_{max} (μmoleq.L^{-1})	i.v.	4.29	0.98	4.54	
	oral	5.53	0.81	5.41	
t_{max} (h)	i.v.			0.67	
	oral			0.50	
AUC_{0-inf} (μmoleq.h.L^{-1})	i.v.	8.95	1.69	9.12	
	oral	11.24	1.74	11.48	
$t_{½}$ (h)	i.v.	1.20	0.24	1.20	
	oral	1.18	0.17	1.08	
		SUM OF PANTOPRAZOLE AND METABOLITES			
c_{max} (μmoleq.L^{-1})	oral	20.34	2.36	20.19	
t_{max} (h)	oral			0.50	
AUC_{0-inf} (μmoleq.h.L^{-1})	i.v.	29.41	5.48	30.61	
	oral	40.53	10.38	37.20	
$t_{½}$ (h)	i.v.	1.04	0.30	1.02	
	oral	1.28	0.20	1.21	

Like the parent drug, the metabolites of pantoprazole are rapidly cleared from the serum.

(c) **Confirmation of Metabolic Pathways**: In *in vitro* studies with human liver microsomes, pantoprazole metabolism was significantly inhibited by ketoconazole, quinidine and sulfaphenazole, confirming the participation of CYP3A4 and/or CYP2C19, CYP2D6 and CYP2C9, respectively, in the metabolic process (Byk Gulden Protocol 120/96; GTR 31216). Lower rates of pantoprazole metabolism were observed for CYP2C19 poor metabolizers and CYP3A4 medium metabolizers but not for CYP2D6 poor metabolizers. These findings confirm the participation of CYP2C19 in pantoprazole and suggests this isozyme' (CYP2C19) and/or CYP3A4 to be the major isozyme(s) responsible for pantoprazole metabolism. The results of the above *in vivo* metabolism study (Byk Gudlden Protocol #FHP018E, GMR-29693) indicates that CYP2C19 is the major isozyme responsible for the metabolism of the drug.

5. PHARMACOKINETICS OF PANTOPRAZOLE ENANTIOMERS: Pantoprazole is a racemic compound with the center of optical activity at the sulfur atom. In the NDA, it is stated the pharmacologic activities of its enantiomers are "indistinguishable. However, toxicology studies in animals have shown that the (-)-enantiomer is more toxic than the (+)-enantiomer and that only the (+)-enentiomer converts to the (-)-enantiomer. The kinetics of the (+)- and (-)-enantiomers was evaluated in (i) 8 extensive metabolizers (selected from Protocol HFP016) receiving a single 80 mg dose of pantoprazole by intravenous bolus injection, (ii) 9 extensive metabolizers (selected from Protocol FHP014) receiving a single 40 mg (2x20 mg enteric coated tablets) oral dose and (iii) one poor metabolizer (Subject 1 from Protocol HFP006, pantoprazole $t_{1/2}=6.4$ h) receiving a single 30 mg dose by intravenous bolus injection and three poor metabolizers (Subject 22 from HFP014 with pantoprazole $t_{1/2}=6.3$ h and Subjects 9 and 12 from Protocol FHP017 with pantoprazole $t_{1/2}$ values of 4.2 h and 4.6 h, respectively) each receiving a single oral dose of the enteric coated 40 mg tablet (Byk Gulden Report 227/92; GMR-30131). Mean plots were not provided. Typical individual subject plots of serum concentration versus time for the racemic ($\pm$) [unresolved] pantoprazole and its (+)- and (-)-enantiomers are presented in Figs. 13-16 for these subject groups. The mean $\pm$ SD pharmacokinetic parameters of these moieties in these sub-populations are presented in Table 12. IV, PO, NM and EM, represent intravenous administration, oral administration, normal metabolizer and poor metabolizer, respectively.

Fig 13. Typical Individual Subject Plots of Serum Concentrations of Racemic Pantoprazole and its (+)- and (-)-Enantiomers Following Intravenous Administration of 80 mg Racemic Pantropazole in Normal Metabolizers

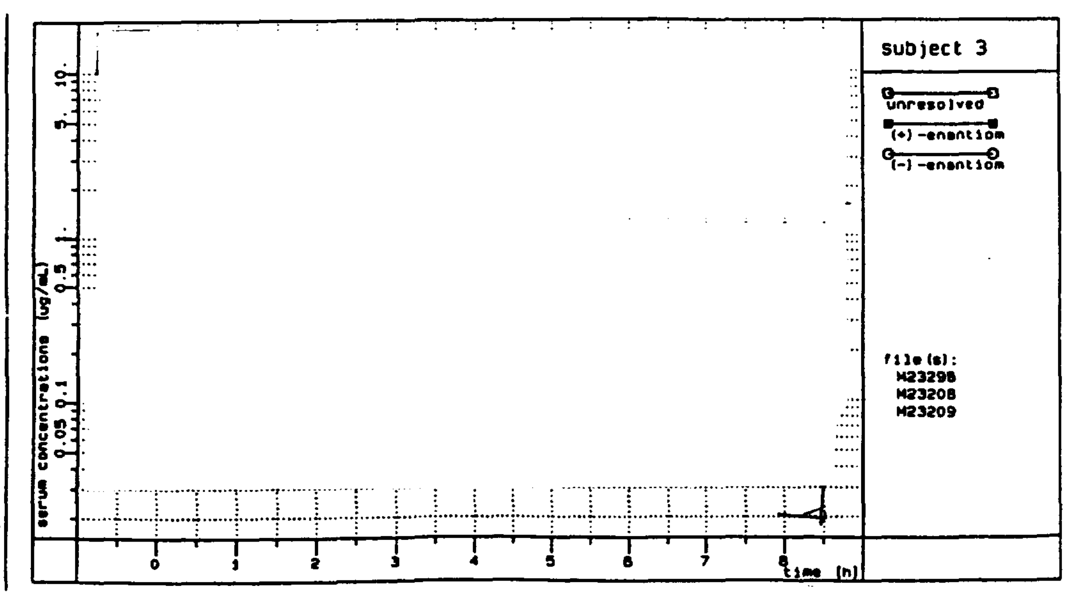


Fig 14. Typical Individual Subject Plots of Serum Concentrations of Racemic Pantoprazole and its (+)- and (-)-Enantiomers Following Oral Administration of 40 mg Racemic Pantropazole in Normal Metabolizers

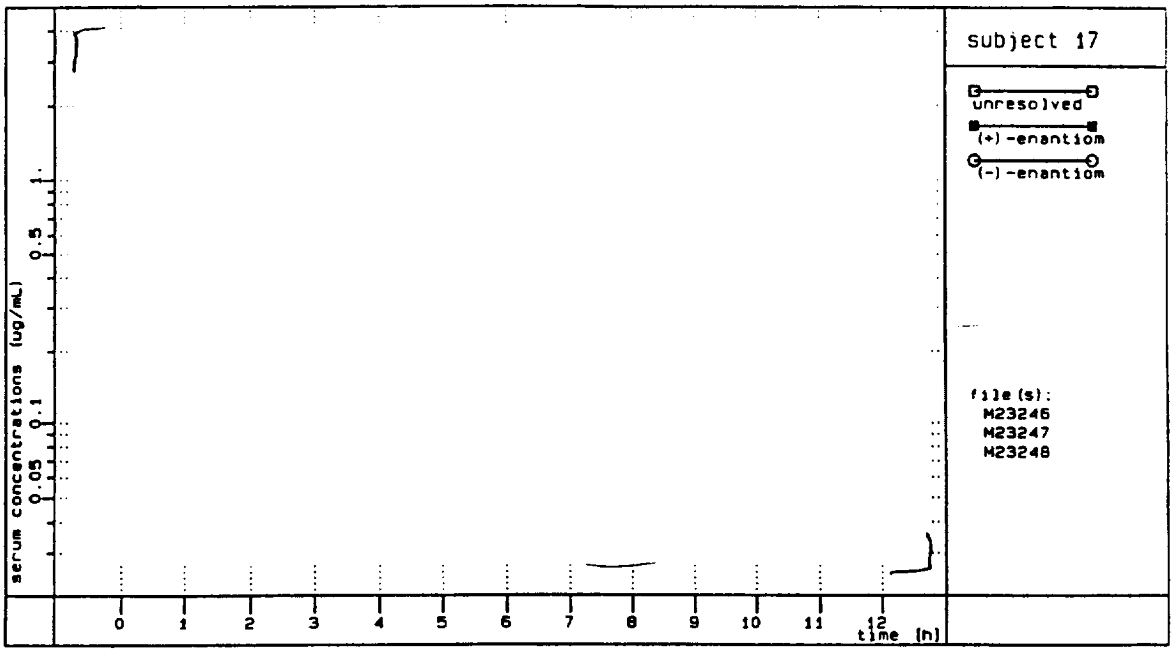


Fig 15. Typical Individual Subject Plots of Serum Concentrations of Racemic Pantoprazole and its (+)- and (-)-Enantiomers Following Intravenous Administration of 30 mg Racemic Pantropazole in Poor Metabolizers

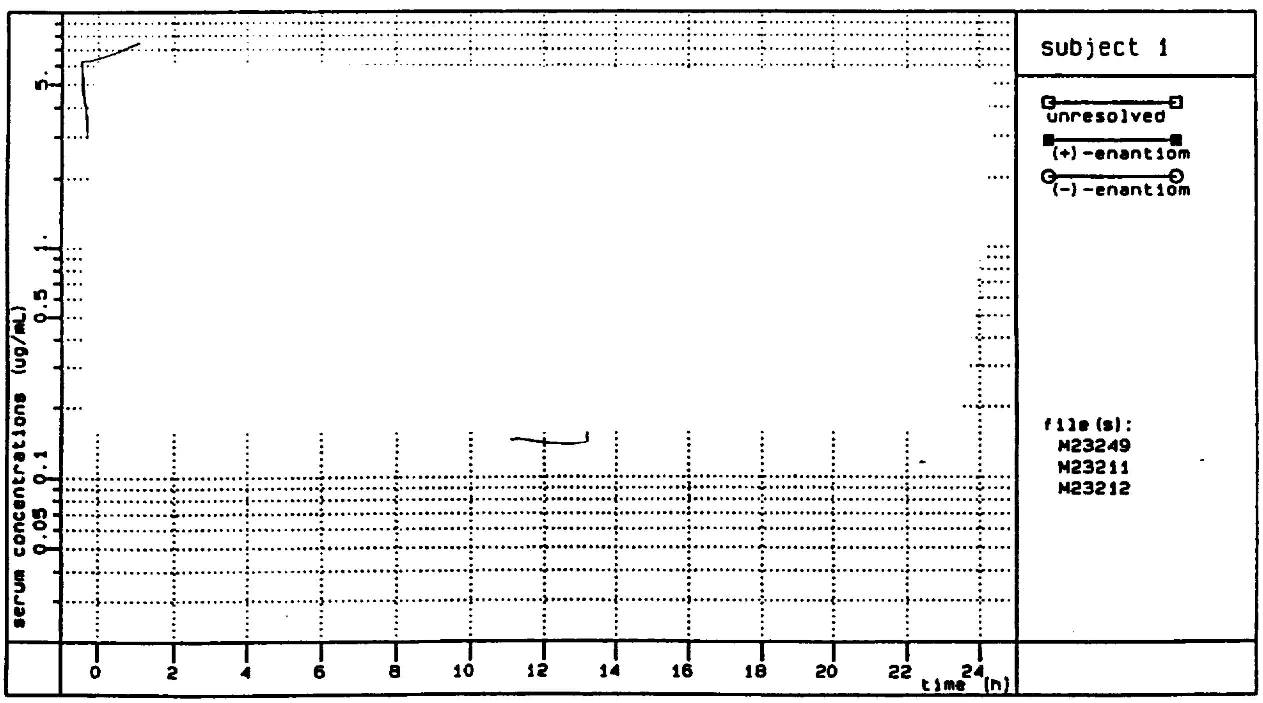


Fig 16. Typical Individual Subject Plots of Serum Concentrations of Racemic Pantoprazole and its (+)- and (-)-Enantiomers Following Oral Administration of 40 mg Racemic Pantropazole in Poor Metabolizers

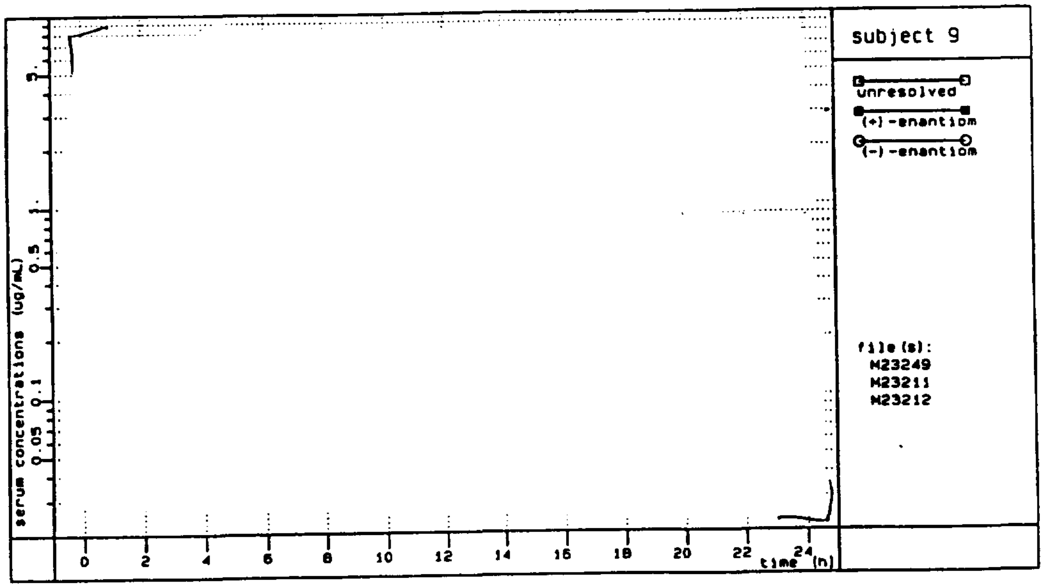


Table 12. Pharmacokinetic Parameters of Racemic Pantoprazole and its (+)- and (-)-Enantiomers Following Intravenous and Oral Administration in Normal Metabolizers and Poor Metabolizers

Moiety	n	Dose (mg)	C_{max} (mg/L)	t_{lag} (h)	t_{max} (h)	AUC ([mg/L]h)	$t_{1/2}$ (h)	Cl_T (L/h)	V_d (L)
±	8(EM)	80(IV)	----	----	----	9.3±3.8	1.2±0.6	10.0±4.1	17.5±12.4
(+)-	8(EM)	-----	----	----	----	4.3±2.0	0.9±0.5	22.3± 10.0	28.7±21.4
(-)-	8(EM)	----	----	----1	----	4.8± 3.2	1.1±0.5	19.4±8.2	29.4±22.9
±	9(EM)	40(PO)	2.7+1.1	----	2.4+1.1	5.8±3.0	1.3±0.3	----	----
(+)-	9(EM)	----	1.4+0.5	----	2.8+1.0	3.1±1.8	1.0±0.5	----	----
(-)-	9(EM)	----	1.4+1.1	----1	2.4+1.1	3.1± 1.4	1.1±0.4	-----	----

In extensive metabolizers, regardless of the route of administration (intravenous or oral), the elimination of the (+)-enantiomer ie essentially the same as the (-)-enantiomer but in general, the pharmacokinetic parameters of both species were comparable. In poor metabolizers, the elimination half-life for the (+)- enantiomer more than doubled and its AUC (where determined) more than tripled the values for the (-)-enantiomer. In three of the four poor metabolizers, the elimination half-life values for the (-)-enantiomer (2.5-2.8 h) were within the range ($\leq$ 3.5 h) specified in the NDA for extensive metabolizers of pantoprazole. The value for the remaining one subject (3.9 h) was close to this range. It was further noted that in the serum of extensive metabolizers, the percentage of pantoprazole in the form of the (+)-enantiomer generally decreased with time and was less than 50% of total pantoprazole by 7 h postdose regardles of the route of administration (Figs. 17 and 18). The reverse was true of poor metabolites, with the percentage of pantoprazole in the form of the (+)-enantiomer being approximately 80-90% of total pantoprazole in serum in the interval of 12-24 h postdose (Fig. 19).

Fig. 17. Percentage of (+)-Enantiomer in Serum Following Intravenous Administration of 80 mg Racemic Pantoprazole in Extensive Metabolizers

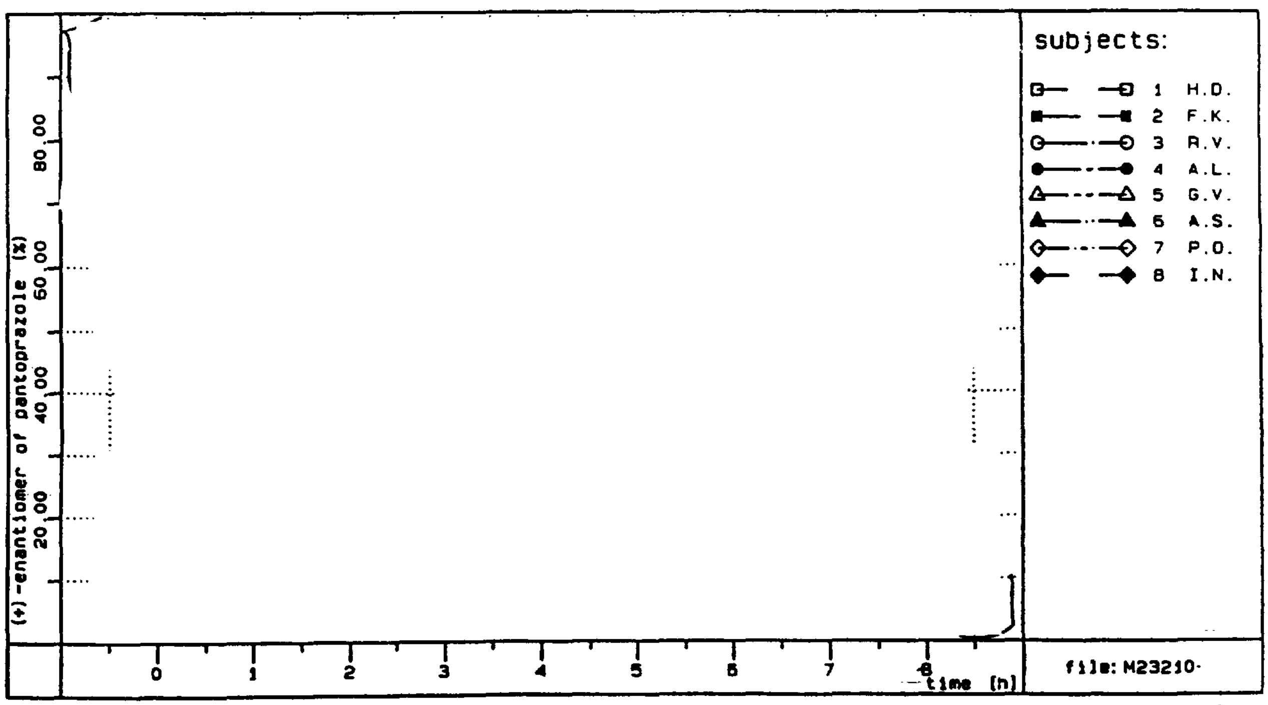


Fig.1: percentage (%) of (+)-enantiomer of pantoprazole in serum after the first i.v. bolus injection of 80 mg pantoprazole to healthy volunteers

Fig. 18. Percentage of (+)-Enantiomer in Serum Following Intravenous Administration of 40 mg Racemic Pantoprazole in Extensive Metabolizers

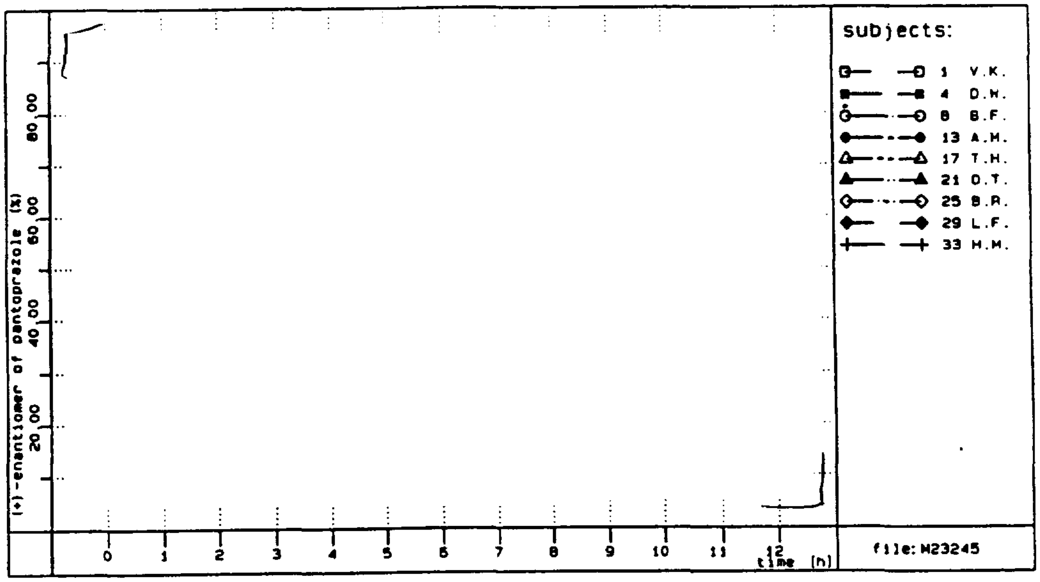
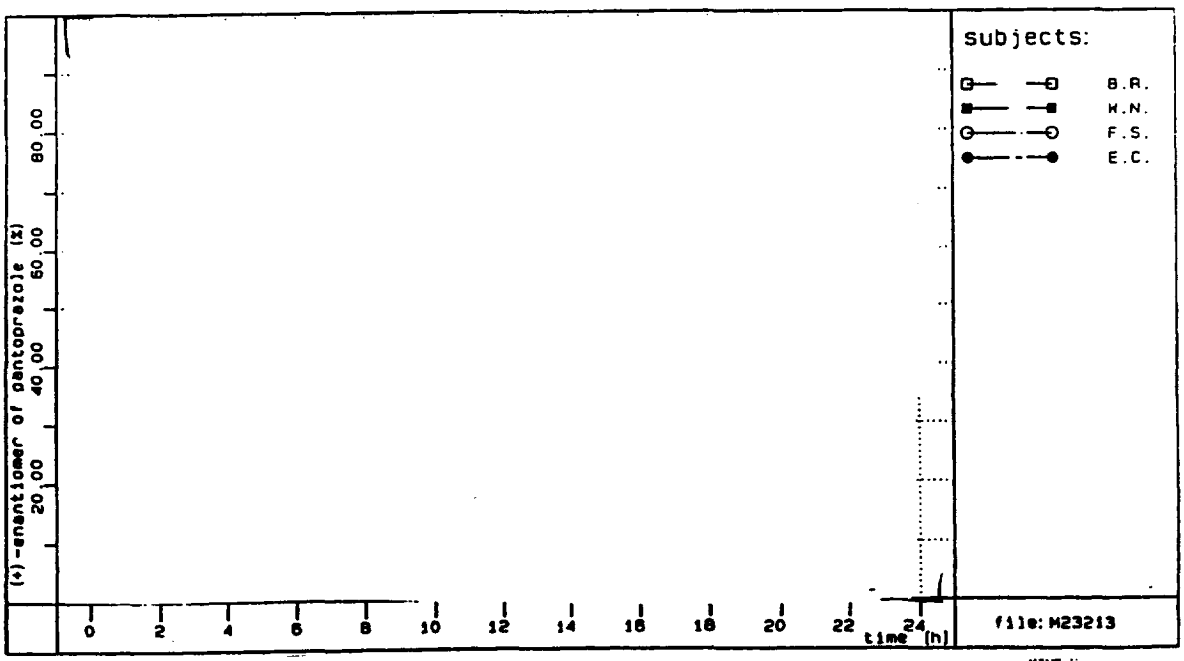


Fig. 19. Percentage of (+)-Enantiomer in Serum Following Intravenous 30 mg and Oral 40 mg Racemic Pantoprazole in Poor Metabolizers



These findings suggest that only the metabolism of the (+)-isomer of pantoprazole is significantly affected by the genetic polymorphism exhibited by CYP2C19, the major isozyme for pantoprazole metabolism.

6. PRE-SYSTEMIC ELIMINATION: In a crossover study of intravenous and oral solution doses of ^{14}C-pantoprazole in six healthy volunteers (Byk Gudlden Protocol #FHP018E, GMR-29693), the absolute bioavailability of pantoprazole for the oral solution was 81% whereas 96% of the dose was absorbed. It is reasonable to infer that the difference in the absorbed and bioavailable amounts (15% of the oral dose) is due pre-systemic metabolism. The higher amounts of pantoprazole metabolites at 8 and 24 h postdose for the oral dose as compared to the intravenous dose (see item 4 [page 19]) also suggests the occurrence of pre-systemic metabolism.

7. BINDING TO ERYTHROCYTES: In the above crossover study of intravenous and oral solution doses of ^{14}C- pantoprazole in six healthy volunteers (Byk Gudlden Protocol #FHP018E, GMR-29693), the geometric mean $\pm$ SD ratio ($AUC_{serum}/AUC_{whole\ blood}$) of total radioactivity was high (1.66 ± 0.66 for oral solution and 1.59 ± 0.15 intravenous administration). These results suggest that erythocyte binding or penetration of pantoprazole is minimal to negligible as compared to it binding to serum components. These findings are supported by the 98% binding to serum components determined in the serum protein binding studies (see item 8).

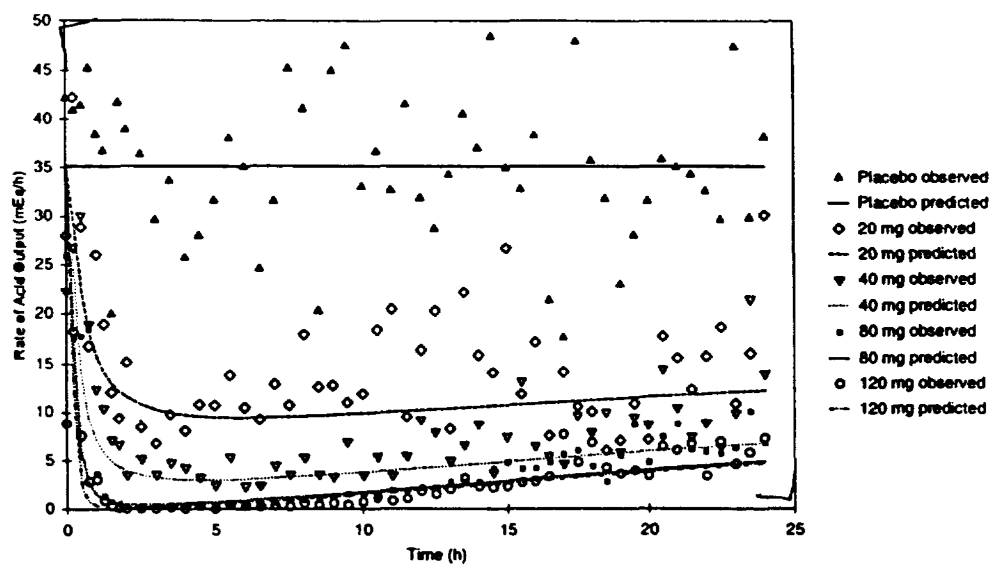
8. SERUM PROTEIN BINDING: The serum protein binding of pantoprazole was determined (i) in serum obtained from five healthy male subjects injrcted with ^{14}C-labeled pantoprazole (^{14}C-pantoprazole), (ii) in 3.5% human albumin and (iii) in 0.2% alpha1-acid glycoprotein at pantoprazole concentrations ranging from 0.23 ug/mL to 100.23 um/mL. The method of equilibrium dialysis was utilized (Byk Gulden #RZ93002/BY1023). Pantoprazole was 97% bound to serum proteins at all concentrations tested, 94% bound to serum albumin in the concentration range of 0.23 - 20.23 um/mL and 91% bound to serum albumin at a concentration of 100.23 ug/mL. Pantoprazole binding to $alpha_1$-glycoprotein (64%, 50%, 31% and 15% at concentrations of 0.23, 2.23, 20.23 and 100.23%, respectively) was drug concentration dependent. These results suggest the presence of multiple pantoprazole binding sites on $alpha_1$-glycoprotein. *In vitro* study of pantoprazole binding to human serum proteins by the method of equilibrium dialysis was estimated in two other studies, Byk Gulden Report #244E/88 (five pantoprazole concentrations in the range of 0.9-9.8 umol per liter) and Byk Gulden Report #90E/96 (pantoprazole concentrations of 0.5 and 3.0 ug/mL) . In both studies pantoprazole was 98% bound to human serum proteins. Pantoprazole was also 98% bound to serum proteins of renally impaired patients receiving a single dose of the 40 mg enteric coated tablet (Byk Gulden Protocol FHP023).

Based on these findings, (i) pantoprazole is highly bound to human serum proteins, (ii) the primary serum binding protein is serum albumin and (iii) $alpha_1$-glycoprotein plays only a minor role in the binding of pantoprazole and may have multiple binding sites for it.

9. PHARMACODYNAMICS: Pantoprazole is a non-competitive inhibitor of the proton pump which suppresses the final step in gastric acid secretion by binding covalently to the (H+,K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell.

10. PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) RELATIONS: The relationship between the pharmacokinetics and pharmacodynamics .of pantoprazole was evaluated for the 0 (placebo), 20, 40, 80 and 120 mg doses of pantoprazole administered by intravenous infusion, over 15 min, to normal subjects in whom gastric acid secretion was induced using pentagastrin (Protocol 3001k1-100-US). The irreversible effect pharmacodynamic model was utilized. Since drug concentrations were not measured in this study, the pantoprazole concentrations obtained for the 20, 40 and 80 mg doses in another study (Byk Gulden Protocol FHP003) and those predicted for the 120 mg dose using the data from Byk Gulden Protocol FHP003 (assuming dose proportionality in the pantoprazole dose range of 20-120 mg) were used to build the model The results are presented in Fig. 20.

Fig. 20. Pharmacodynamic Profile of Pantoprazole



In Byk Gulden Protocol FHP003, dose proportionality of Cmax and AUC for single dose administration was demonstrated for the dose range of 20-80 mg. The 120 mg dose was not evaluated. Therefore, in this review, the assumption of dose proportionality in the dose range of 20-120 mg is not considered to be tenable. Accordingly, the data for the 120 mg dose is not considered in discussing the results.

The 20 mg and 40 mg doses of intravenous pantoprazole reduced pentagastrin induced gastric acid output from the placebo value of 35 MEq/h to approximately 10 mEq/h and 2.5 mEq/h, respectively. With the 80 mg dose, pentagastrin induced acid secretion was completely eliminated within 2 h of dosing. In this study, pantoprazole reduced pentagastrin induced acid secretion in a dose dependent fashion.

The effect of pantoprazole on gastric acid reduction lasts about 24 h which supports the dosing interval of 24 h.

In a placebo controlled, clinical efficacy trial that used enteric coated pantoprazole tablets at doses of 20, 40 and 80 mg, the median intragastric pH values for the 40 and 80 mg doses were similar but were significantly lower than the values for the 20 mg dose (Table 13). These findings suggest that the 80 mg dose would have no significant therapeutic advantage over the 40 mg dose, which was ultimately selected for marketing.

Table 13. Effects of Single 20, 40 and 80 mg Doses of Pantoprazole On Intragastric pH as Compared to Placebo

	Median pH			
Time	placebo	20 mg	40 mg	80 mg
8 a.m. - 8 a.m. (24 hours)	1.3	2.9*	3.8*#	3.9*#
8 a.m. - 10 p.m. (Daytime)	1.6	3.2*	4.4*#	4.8*#
10 p.m. - 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

* Significantly different from placebo
\# Significantly different from 20 mg

11. EFFICACY END POINT: HEALING OF EROSIVE ESOPHAGITIS ASSOCIATED WITH REFLUX DISEASE (GERD): The rate of GERD healing was assessed at the end of 4 and 8 weeks of treatment in 541 patients receiving the enteric coated 10, 20 and 40 mg pantoprazole tablets for 8 weeks in a placebo controlled efficacy trial (n=68, 153, 158 and 162 for placebo, 10, 20 and 40 mg doses, respectively). The healing rates for 4 and 8 weeks of treatment are presented in Table 14.

Table 14. Erosive Esophagitis Healing Rates for Oral 10, 20 and 40 mg Oral Pantoprazole Treatment of Patients with GERD as Compared to Placebo

Erosive Esophagitis Healing Rates

	PROTONIX			Placebo
Week	10 mg QD (n = 153)	20 mg QD (n = 158)	40 mg QD (n = 162)	(n =68)
4	45.6%+	58.4%+#	75.0%+*	14.3%
8	66.0%+	83.5 %+#	92.6%+*	39.7%

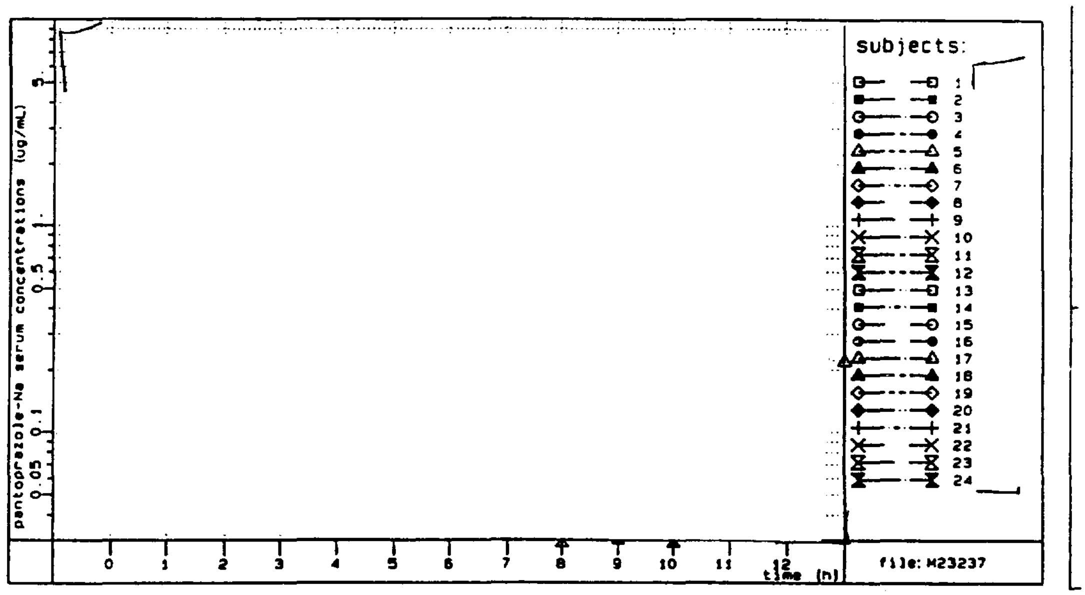
+(p < 0.001) PROTONIX versus placebo.
*(p <0.05) versus 10 mg, or 20 mg PROTONIX
\# (p<0.05) versus 10 mg PROTONIX

For the evaluated dose range of pantoprazole, erosive esophagitis healing rate increased significantly with increasing pantoprazole dose. The healing rate for the 40 mg dose was considered optimal.

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)

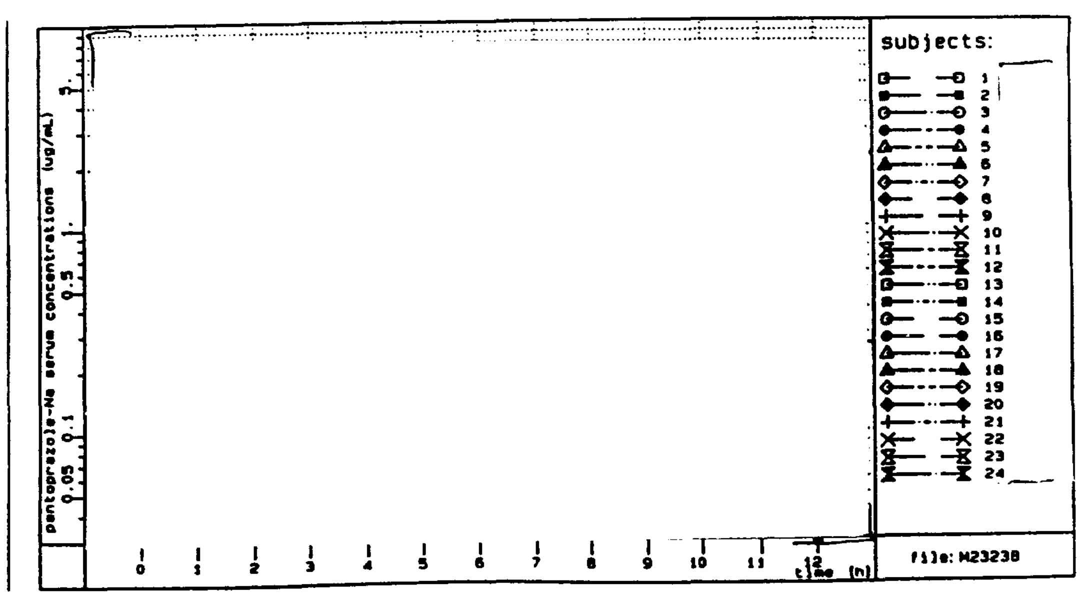


Table 15. Mean + SD Pharmacokinetic Parameters of Pantoprazole Following Single Oral 40 mg Enteric Coated Tablet Dose in Normal Subjects under Fasted Conditions and Just Before Breakfast

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	Test: with food	Equivalence ratio (Test/Reference) Point estimate	90%-confidence interval	
	Geometric mean, n=19 (n=23 for tmax-tlag) exp (mean(ln) ± SD (ln)) $)		after logarithmic transf.$)		
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
t½ (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

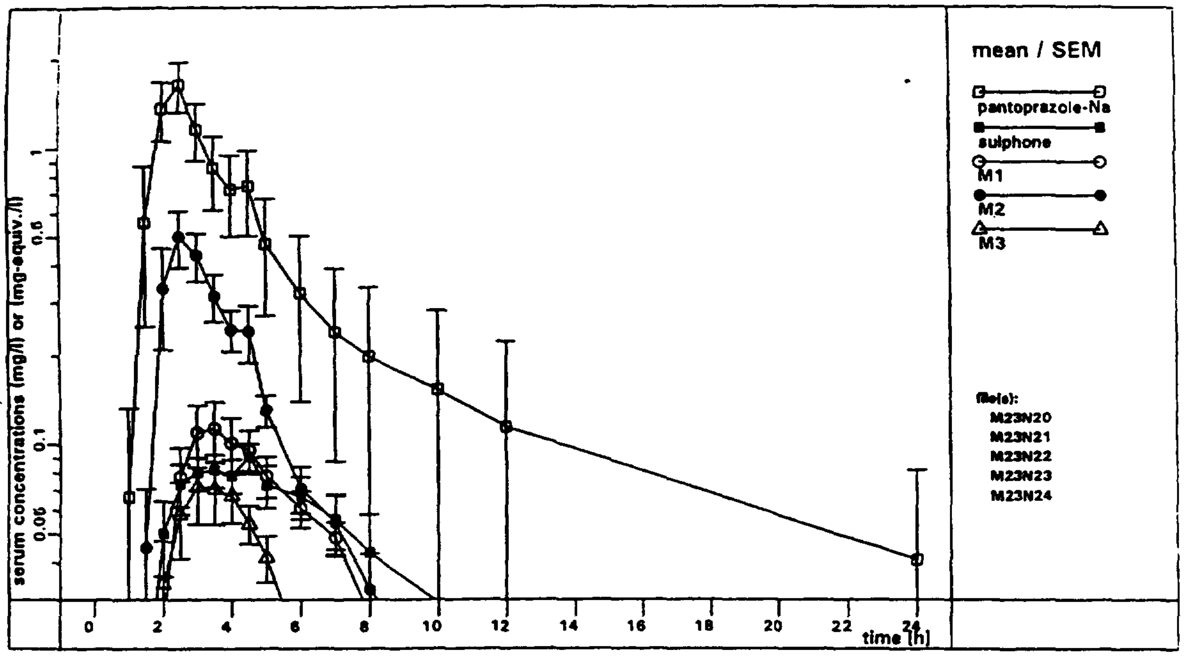
Pantoprazole t_{lag}, t_{max} and $t_{1/2}$ for males and females were comparable with or without food in the stomach. However, the mean C_{max} (without food), C_{max} (with food) and AUC (without food [not normalized for body weight]) for females were 25%, 28% and 46%, respectively, greater than the 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)

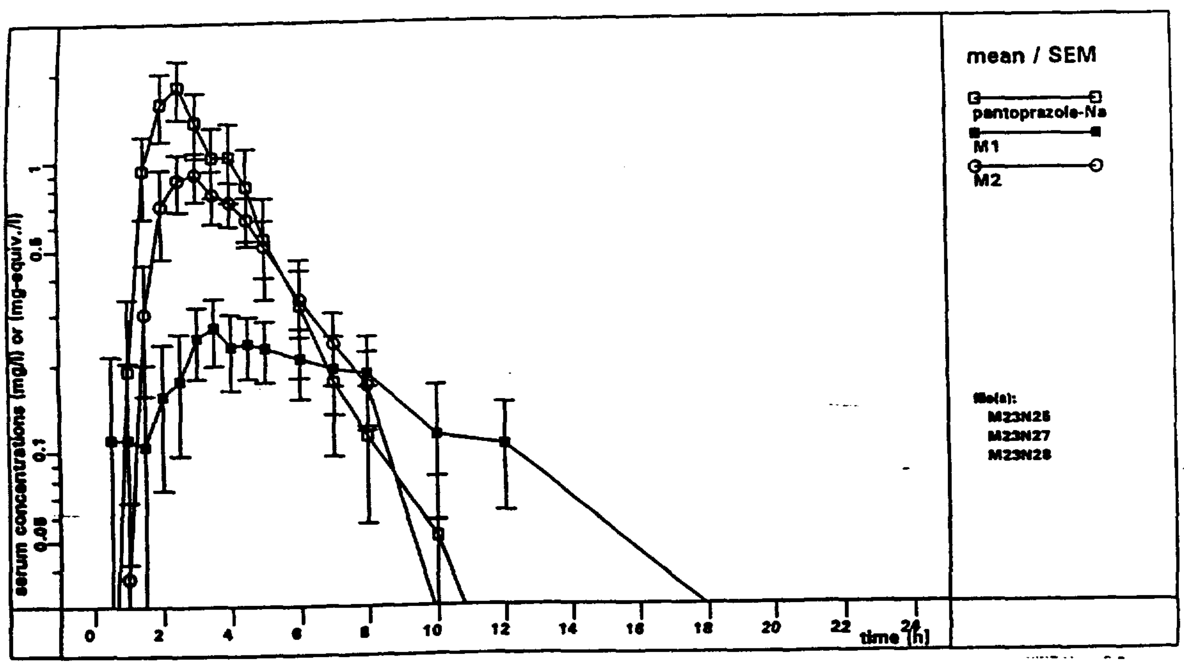


Table 18. Mean ± SD Pharmacokinetic Parameters of Pantoprazole and its M2 Metabolite Following Single Oral Dose of the 40 mg Enteric Coated Tablet Dose in Normal Subjects and Patients with Severe Renal Impairment

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 $\pm$ 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

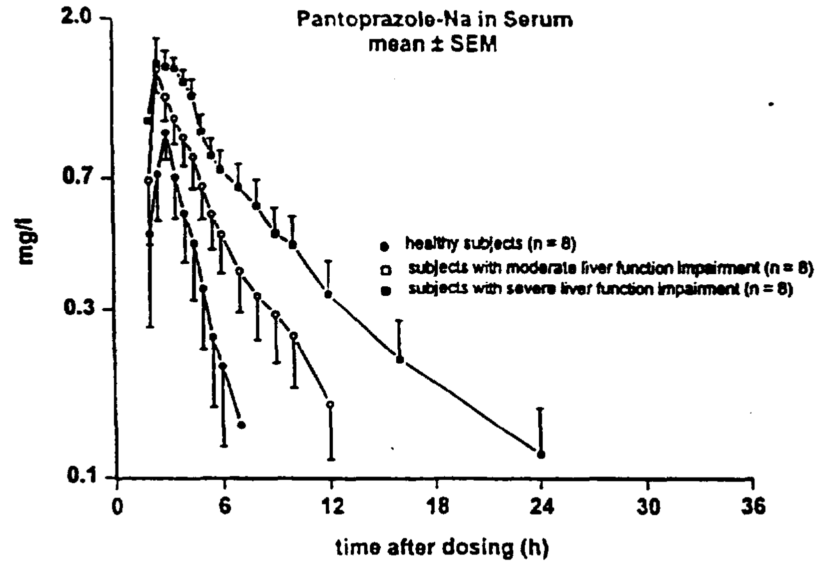


Fig. 24(a). Plots of Mean $\pm$ SEM Serum Concentration of Pantoprazole and its Sulfone Metabolite Versus Time in Subjects with Liver Cirrhosis Following a Daily Intravenous Dose of 30 mg for Five Days

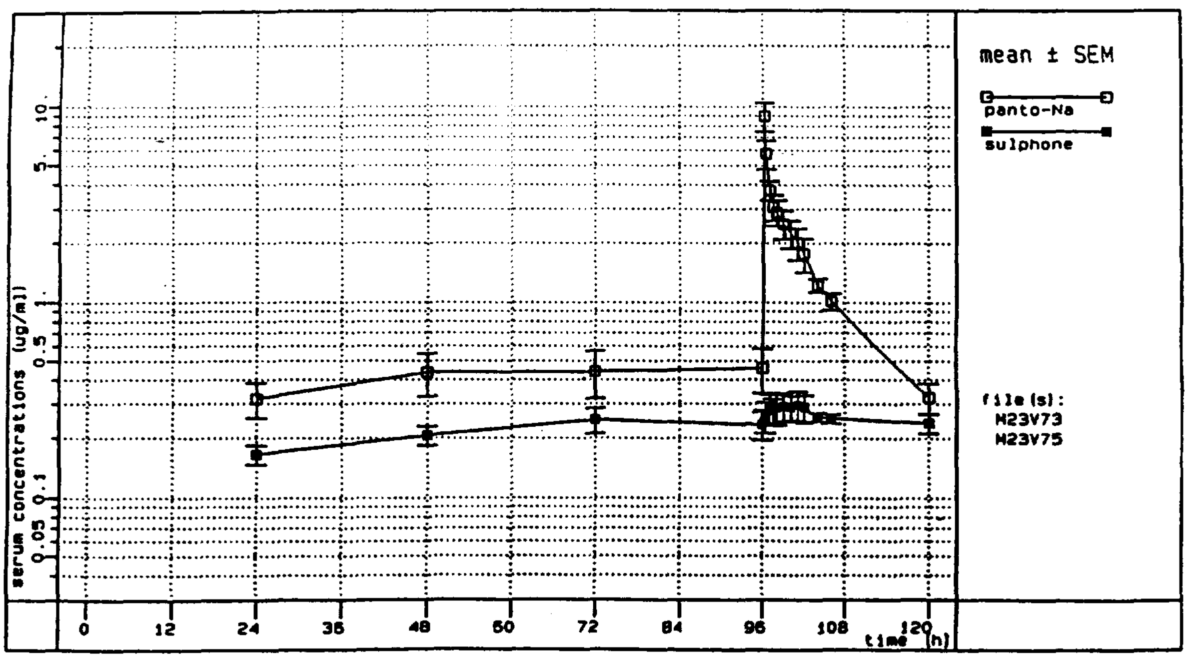


Fig. 24(b). A Plot of Mean $\pm$ SEM Serum Concentration of Pantoprazole and its Sulfome Metabolite Versus Time in Subjects with Liver Cirrhosis Following a Daily Oral Dose of the 40 mg Tablet for Seven Days

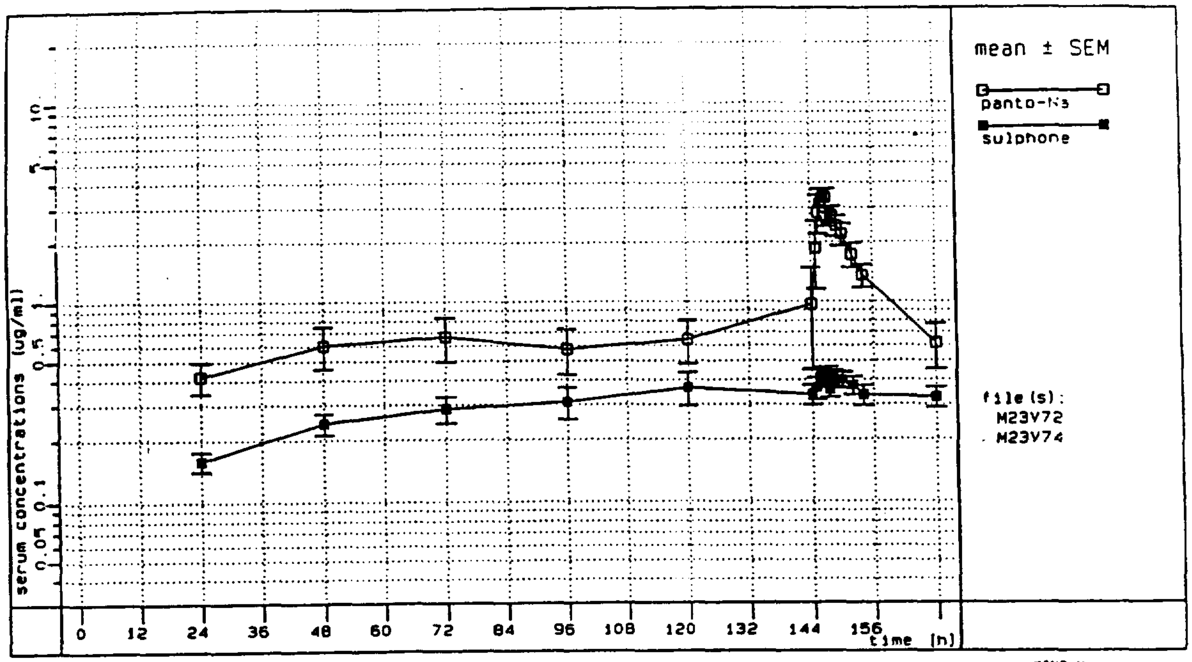


Table 19. Mean + SD Pharmacokinetic Parameters of Pantoprazole Following a single Oral 20 mg Enteric Coated Tablet in Nprmal Subjects and Patients with Moderate and Severe Hepatic Impairment and the Oral 40 mg Enteric Coated Tablet Dose or 30 mg Intravenous Dose in Patients with Liver Cirrhosis.

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

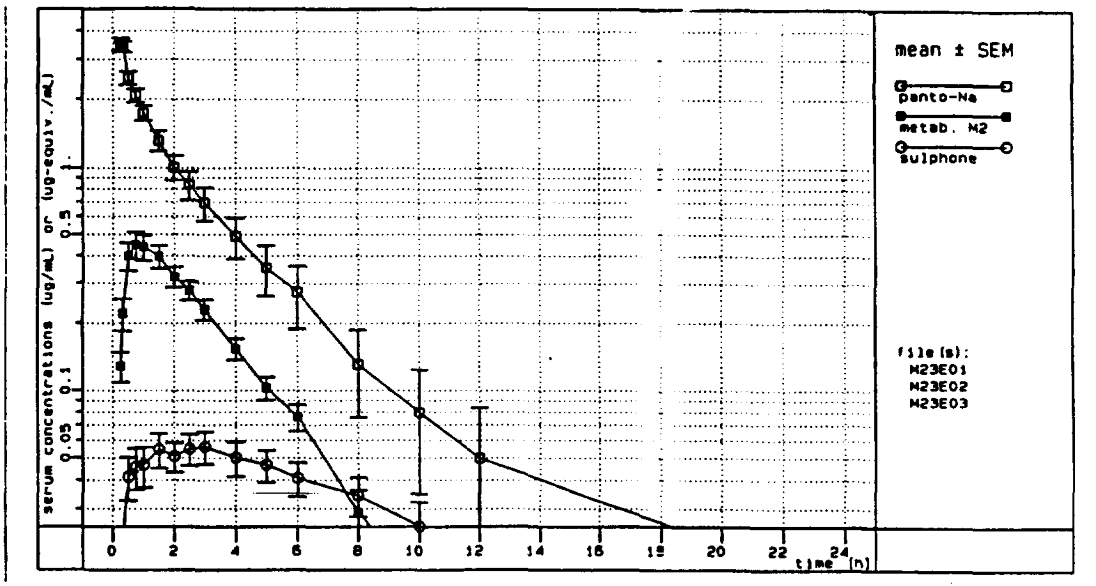
For the single, 20 mg dose regimen, the elimination half-life and AUC of pantoprazole increased significantly in the order of SHI>MHI>NV. Mild increases, in the same order, were also noted for C_{max}. For the multiple dose study in patients with cirrhosis, the mean ($\pm$ SD) steady state C_{max} for the 40 mg oral dose (4.22$\pm$1.61 ug/mL [n=7]) was comparable to the mean value for the 80 mg oral dose in healthy, extensive metabolizers of pantoprazole (4.09$\pm$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 $\pm$ 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)

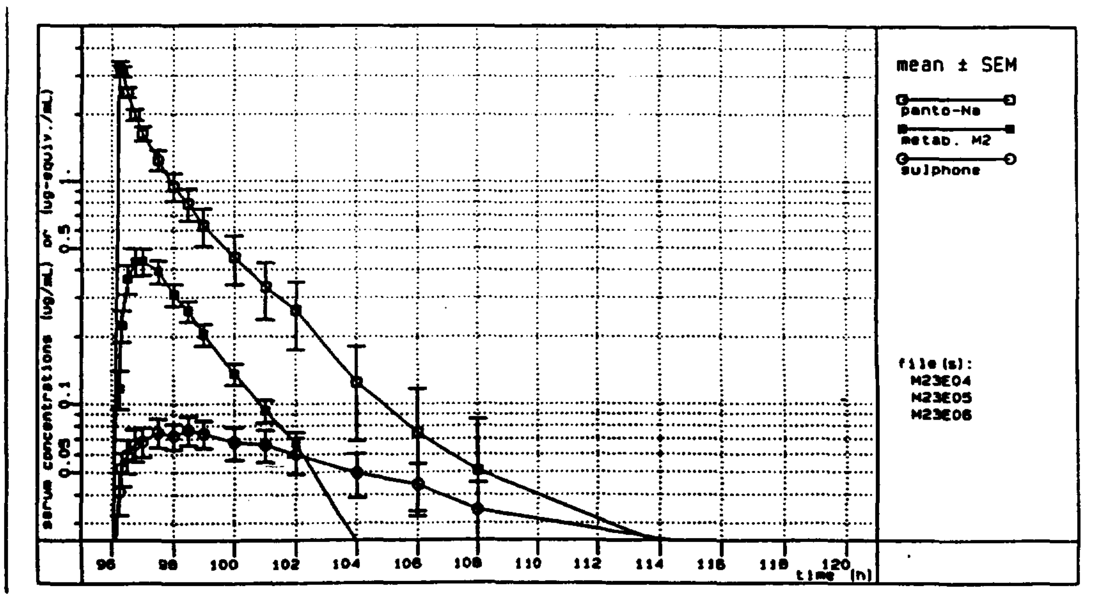
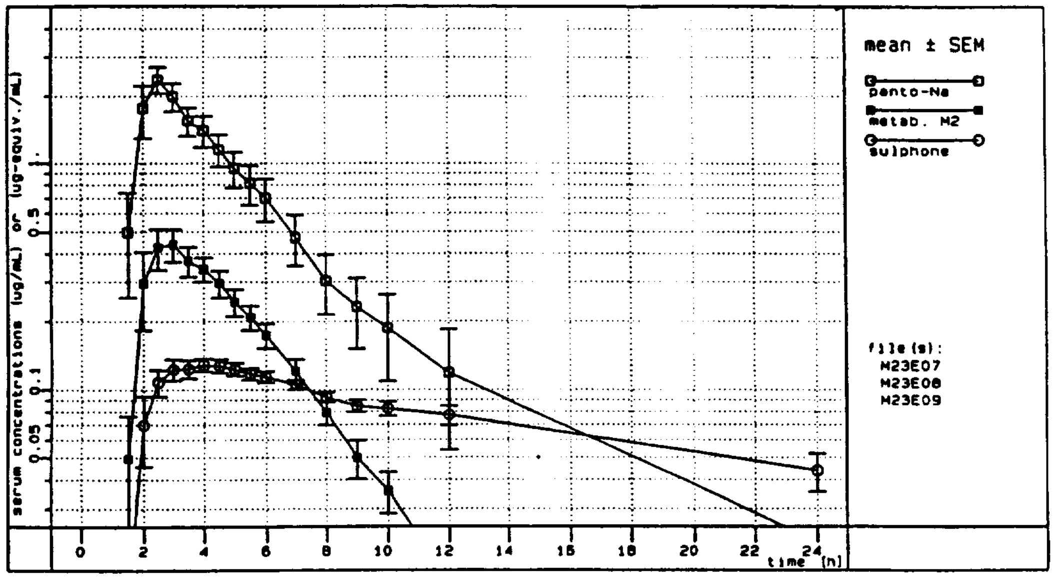


Fig. 26. Plots of Mean ± Serum Concentration of Pantoprazole and its M2 and Sulfone Metabolites Versus Time in Healthy, Elderly Subjects on Day 1 (a) and Day 7 (b) Following a Daily Oral Dose of 40 mg for Five Days (From Byk Gulden Protocol FHP017/E)

(a)



(b)

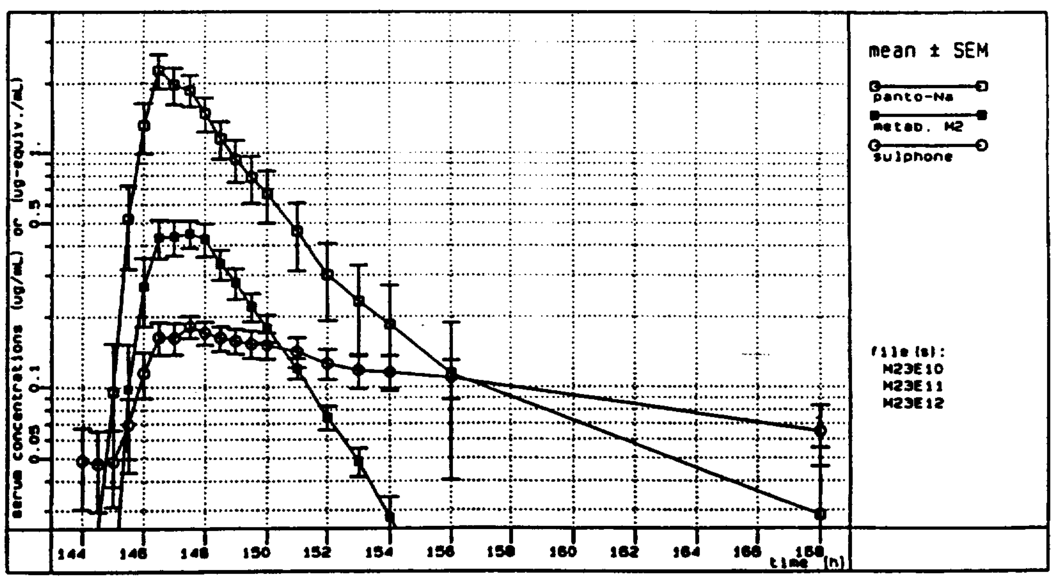
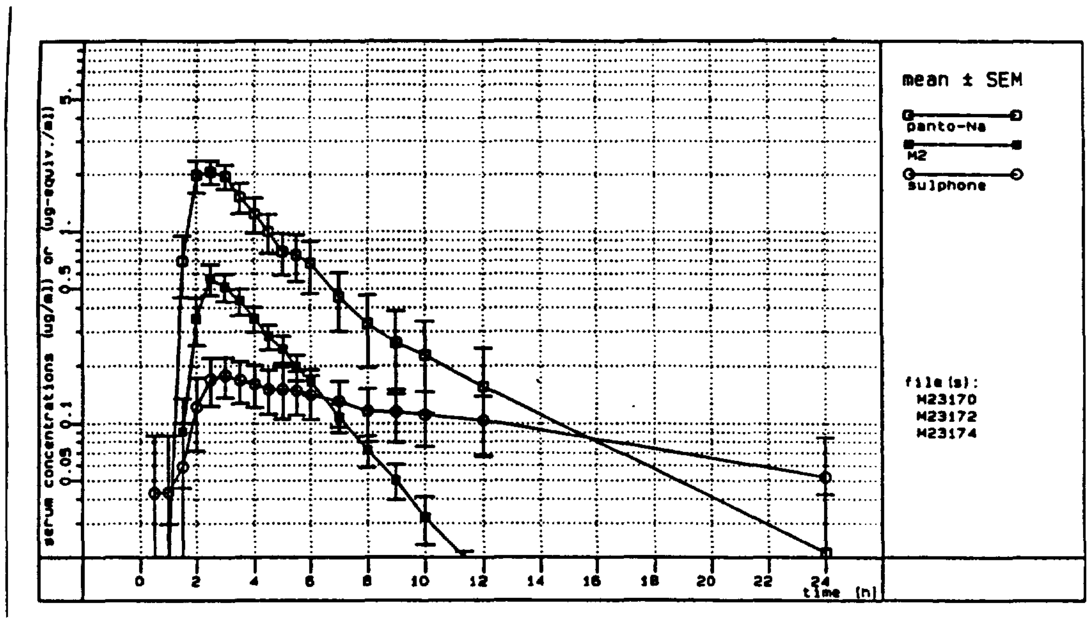


Fig. 27. Plots of Serum Concentration of Pantoprazole and its M2 and Sulfone Metabolites Versus Time in Healthy, Elderly Subjects on Day 1 (a) and Day 7 (b) Following Daily Intravenous Dose of 40 mg for Seven Days (From Byk Gulden Protocol FHP017E)

(a)



(b)

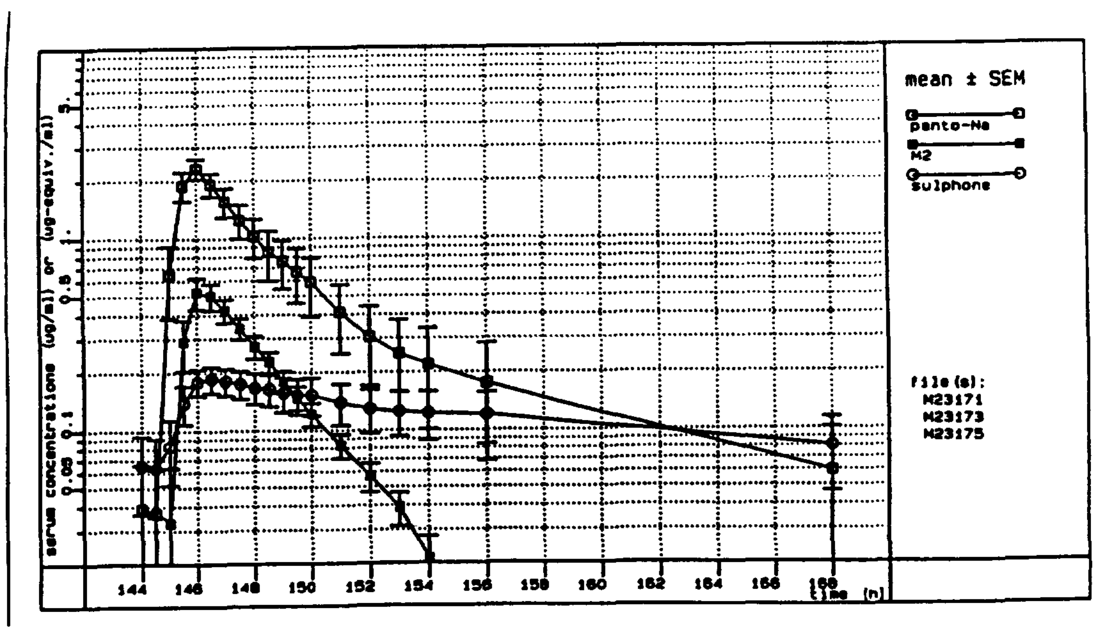


Table 20. Mean ± SD Pharmacokinetic Parameters of Pantoprazole Following Oral Doses of the 40 mg Enteric Coated Tablet for Seven Days and 30 mg doses by Intravenous Infusion for Five Days in Healthy Elderly Subjects

Protocol	Day	n	Dose (mg)	C_{max} (ug/mL)	t^{lag} (h)	t_{max} (h)	AUC (mg/L)h	$t_{½}$ (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 21 (contd.). Mean ± SD Pharmacokinetic Parameters of Pantoprazole with and without Concomitantly Administered Drugs

Diclofenac (100 mg)										
FHP025	1	23(S)	40(PO)	3.15±1.06	1.7±0.8	2.6±0.9	6.0±3.5	1.1±0.3	----	----
	1	24(C)	40(PO)	3.15±1.17	1.6±0.8	2.6±0.8	6.0±3.0	1.1±0.3	----	----
Maalox™ (10 mL)										
FHP021	1	22(S)	40(PO)	3.38±1.36	1.2±0.6	2.3±0.8	6.0±3.5	1.2±0.5	----	----
	1	1(S[pm])	40(PO)				41	7.6	----	----
	1	22(C)	40(PO)	3.36±1.11	1.0±0.7	2.0±0.7	6.2±3.5	1.2±0.4	----	----
	1	1(C[pm])	40(PO)				37	7.4	----	----
Digoxin (0.2 mg)										
FHP019	1	18(S)	40(PO)	3.02±1.08	1.8±1.6	2.9±1.6	5.6±2.7	1.0±0.2	----	----
	5	18(C)	40(PO)	2.88±0.73	1.3±0.6	2.4±0.6	5.2±2.1	1.0±0.2	----	----

The kinetics of pantoprazole was not significantly affected by concomitant administration of any of the above drugs. Since CYP2D6 plays only a minor role in the metabolism of pantoprazole, drugs metabolized by this isozyme are also not expected to significantly affect its kinetics. These findings suggest that drugs with the same metabolic pathways as pantoprazole, as well as antacids and digoxin, may not significantly alter its kinetics. Therefore, adjustment of the doses of such drugs for patients treated with pantoprazole is not necessary.

(b) **Effect of Pantoprazole on the Kinetics Co-administered Drugs**: The effects of pantoprazole on the kinetics of co-administered drugs was evaluated in normal volunteers receiving the co-administered drug with and without pantoprazole in crossover studies. For each study, the protocol number and a summary of the pharmacokinetic parameters of the co-administered drug are presented in Table 22. 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 22. Mean ± SD Pharmacokinetic Parameters of Selected Drugs with and without Concomitant Administration of Pantoprazole

Protocol	Day	n	Dose(P) (mg)	C_{max} (ug/mL)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)	Cl_T (L/h)	V_d (L)
Diazepam (0.1 mg/kg[IV])									
FHP004E	4	12(S)	240(IV)	—	—	5.0±1.4	41±10	1.4±0.3	81±24
	4	12(C)	240(IV)	—	—	5.0±1.7	37±5.6	1.4±0.4	75±28
Desmethyl-		12(S)		0.03±0.01	64±12	2.6±0.7	—	—	—
Diasepam		12(C)		0.04±0.02	53±38	2.8±1.2	—	—	—
Phenytoin (300mg)									
FHP026E									
	1	23(S)	40(PO)	3.7±0.6	6.2±3.3	126±40	12.6±3.9	—	—
	4	23(C)	40(PO)	3.5±0.8	7.5±5.9	126±43	12.5±3.5	—	—

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	---	---
Cisapridel (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 25 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)			
Sodium carbonate (mg)			
Mannitol (mg)			
Povidone K90 (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.

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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:

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:

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

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

(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, with or without food in the stomach. 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 ...... should be modified as follows:

The tablet should be swallowed whole, with or without food in the stomach. 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.

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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.

Appendix I is retained in the Office of Clinical Pharmacology and Biopharmaceutics and may be obtained upon request.

/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).

MEMORANDUM

(Rev)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II
Gastrointestinal and Coagulation Drug Section

SEP - 8 1998

Date: Tuesday, September 08, 1998 Rev. date

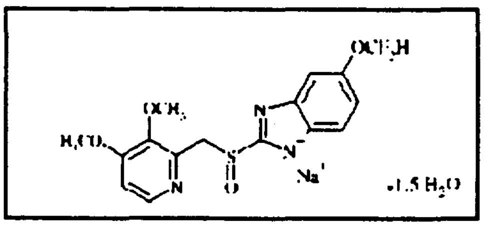
To: Mei-Ling Chen, Ph.D.
John Hunt
David Lee, Ph.D.

From: Alfredo R. Sancho, Ph.D. – Pharmacokinetic Primary Reviewer

Re: 45-Day Pre-filing Meeting for NDA 20-988, Protonix^{TM} I.V. (Pantoprazole Sodium) 40-mg sterile solution.

SUMMARY

Protonix^{TM} or sterile Pantoprazole sodium, 5-(difluoromethoxy)-2-(((3,4-dimethoxy-2-pyridinyl)-methyl)-sulfinyl)-1H-benzimidazole sesquihydrate, is a substituted benzimidazole that functions as an irreversible inhibitor of the gastric H+, K+-ATPase "proton" pump, thereby producing a long lasting reduction of gastric secretion independent of the mode of stimulus. Its empiracal formula is $C_{16}H_{14}F_2NaO_4S$ *x* 1.5 H_2O, with a molecular weight of 432.4. The structural formula is:



Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and it is racemic. Pantoprazole is a weak base and acid. The sodium salt sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane. Pantoprazole serum protein binding is about 98% and is rapidly metabolized with a serum elimination half-life of about 1-hour. The volume of distribution of Pantoprazole is approximately 0.2 L/kg. Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system, primarily CYP-2C19 and CYP-3A4 isozymes. Its metabolism is diminished in patients deficient in CYP-2C19.

The recommended adult intravenous dose is one vial containing the equivalent of 40-mg Pantoprazole sodium given once daily for gastric acid suppression in patients with GERD who are unable to tolerate the oral tablet dosage formulation. The drug is to be administered intravenously over a period of approximately 15-minutes. The sponsor states that no dosage adjustment is necessary in patients with mild, moderate or severe renal insufficiency or in elderly patients. It is also stated in the package insert that no dose adjustment is necessary in patients undergoing hemodialysis, nor patients with mild or moderate hepatic impairment.

Protonix^{TM} I.V. is supplied as a freeze-dried powder in a clear glass vial fitted with a rubber stopper and crimp seal containing the equivalent of 40-mg of Pantoprazole. It is reconstituted with 10-ml of 0.9% Sodium Chloride Injection, USP. The reconstituted solution of Protonix^{TM} I.V. is in the pH range 9.0 to 10.0. The stability of the compound in aqueous solution is pH dependent. The rate of degradation increases with decreasing pH.

OVERVIEW

Background

Pharmacokinetics

The sponsor states that the intravenous Pantoprazole pharmacokinetics seem to be linear and dose proportional over the dose range of 10 to 80 mg and up to 120-mg with limited data. Pantoprazole has a small steady-state volume of distribution (0.2 L/kg) and is rapidly cleared (8 L/h) from the systemic circulation with a $t_{1/2}$ of approximately 1-hour in healthy subjects. Despite the short elimination half-life, Pantoprazole provides dose-related, 24-hour duration of activity, due to its irreversible action on the gastric parietal cell proton pumps. Pantoprazole is metabolized extensively by demethylation (CYP 2C19) and subsequent sulfation and by oxidation/reduction (CYP 3A4) to several inactive metabolites that are mostly renally excreted.

Metabolites

Pantoprazole is metabolized through the cytochrome P450 (CYP) system to a series of metabolites, none of which, according to the sponsor, were found to contribute to the overall pharmacological activity of the parent compound. Metabolites are excreted primarily in the urine and there is no renal excretion of unchanged drug. The main metabolite, M2, which is formed by the CYP 2C19 isozyme, was quantified in most studies along with the sulfone metabolite. The CYP 2C19 isozyme exhibits genetic polymorphism; therefore, the metabolism of Pantoprazole seems to be slower in some subjects ("*poor metabolizers*"). The sponsor identified both the slow-metabolizers and the rapid-metabolizers within the population of these studies. The AUC, t1/2, and CL values for the slow metabolizers were reported separately from those for the normal, rapid metabolizers; the values for the slow metabolizers were marked by the superscript " c".

Drug-Drug interactions

In the present NDA submission, according to the sponsor, there were no pharmacokinetic or pharmacodynamic interactions when Pantoprazole was coadministered with cisapride, ethanol, glibenclamide (glyburide), theophylline, diazepam, phenytoin, carbamazepine, digoxin, warfarin, phenprocoumon, nifedipine, metoprolol, diclofenac, antacids or an oral contraceptive. No drug-to-drug studies were done with antibiotics, which are commonly used in the treatment of *H.pylori*.

Assay Method/s

Safety

Safety was addressed as any clinical adverse experience from all subjects that were enrolled in any of the studies presented in this submission.

SUBMISSION STUDIES

Pantoprazole I.V. doses ranging from 0 to 120-mg over 15-minute infusions were administered. The safety, tolerance, pharmacokinetics and pharmacodynamics of Pantoprazole were examined in 36 Phase I clinical pharmacokinetic studies. A total of 947 volunteers received some form of Pantoprazole, 320 volunteers received a placebo.

Pharmacokinetics

General Pharmacokinetic Studies	
STUDY No.	Description
30137	Single blind, placebo controlled, increasing dose study. To obtain pharmacokinetics of ascending single IV doses of Pantoprazole and to investigate safety, tolerability, and efficacy under pentagastrin infusion.
29693	Single dose, open label, randomized, two period crossover study. To characterize the pharmacokinetics, the absolute bioavailability and the metabolic pathways of Pantoprazole.
30132	Open label, single dose, randomized, two period crossover study. To gain information on the pharmacokinetics, disposition, elimination, bioavailability, and metabolism of Pantoprazole.
30074	Single blind, single dose, randomized, four period crossover study. To study the dose linearity of Pantoprazole pharmacokinetics after IV administration over 15 minutes of therapeutic doses.
30123	Single blind, two period, randomized, crossover, placebo-controlled study. To investigate safety, tolerability, efficacy, and pharmacokinetics of single and repeated IV doses of Pantoprazole and its effect on pentagastrin stimulated gastric acid output.
29727	Double blind, randomized, placebo controlled, two period crossover study. To investigate the efficacy and safety of continuous Pantoprazole infusion in healthy subjects.
30131	To define the pharmacokinetics of both enantiomers after oral and IV administration of racemic Pantoprazole in normal and poor metabolizers.
32020	Randomized, open label, parallel treatment. To compare single doses of Pantoprazole (oral and IV), Famotidine and placebo in inhibition of pentagastrin stimulated acid secretion in healhty subjects.

Special Population Studies

Special Population Studies	
STUDY No.	Description
29733	Randomized, two period crossover study. To assess the PK of Pantoprazole and its M2 and sulfone metabolites following single and multiple oral and IV administration in elderly subjects.
29731	Open label, randomized, two period crossover study. To assess the PK of Pantoprazole and its M2 and sulfone metabolites following single and multiple oral and IV administration of Pantoprazole in elderly subjects.
30125	Single dose, open, randomized, two period crossover study. To study Pantoprazole PK in renal impaired patients before and during hemodialysis.
29700	Single blind, parallel group comparison – healthy volunteers vs. patients with severe renal impairment. To investigate the influence of renal impairment on the PK of Pantoprazole and its M2 metabolite.
31775	Single blind, parallel group comparison – healthy volunteers vs. patients with severe renal impairment. To investigate the influence of renal impairment on the PK of Pantoprazole and its M2 metabolite.
30129	Randomized, multiple dose, two period crossover study. To investigate Pantoprazole PK after repeated oral and IV doses in patients with verified liver cirrhosis.
32398	Open, randomized, parallel group study. To investigate the effect of impaired hepatic function on Pantoprazole PK after a single oral administration.

Bioavailability

Bioavailability/Bioequivalence Studies	
STUDY No.	Description
29728	Single dose, randomized, two period crossover study. To describe the PK of Pantoprazole after oral and IV administration.
29734	Single blind, placebo controlled. randomized, four period crossover study. To investigate the tolerability and PK of Pantoprazole after IV infusion over 15 min of the concentrate or lyophile formulation.

Drug-Drug interactions

Drug Interaction Studies	
STUDY No.	Description
29732	Single dose, randomized, three period crossover study. To investigate the PK interaction between Pantoprazole and antipyrine.
29710	Longitudinal, single and multiple dose Pantoprazole, single dose antipyrine study. To investigate the influence of multiple administrations of Pantoprazole on the kinetics and clearance of antipyrine.
29692	Double blind, randomized, placebo controlled, two period crossover study. To evaluate the influence of oral Pantoprazole on the activities of CYP1A2, N-acetyl transferase (NAT) and xanthine oxidase (XO) enzymes.

31770	Randomized, double blind, placebo controlled, two period crossover study. To evaluate the influence of multiple oral doses of Pantoprazole on ethanol PK profile.
29729	Multiple dose, randomized, open, placebo controlled, two period crossover study. To investigate the PK interaction between Pantoprazole and theophylline after IV administration.
29735	Single blind, placebo controlled, randomized, two period crossover study. To investigate the PK interaction between Pantoprazole and diazepam.
29719	Single blind, randomized, placebo controlled, crossover study. To investigate the influence of Pantoprazole on the PK of carbamazepine.
29691	Bouble blind, placebo controlled, randomized, two period crossover study. To assess the oral PK drug-drug interaction between Pantoprazole and phenytoin.
29698	Single blind, multiple oral dose, randomized, two period crossover. To investigate the PK interaction between Pantoprazole and digoxin.
29698	Single blind, multiple oral dose, randomized, two period crossover study. To investigate the PK interaction between Pantoprazole and digoxin.
32411	Double blind, multiple doses, randomized, two period crossover study. To investigate the PK interaction between Pantoprazole and metoprolol.
29712	Open, randomized, three period crossover study. To investigate at steady state the PK interaction between Pantoprazole and nifedipine and between omeprazole and nifedpine.
30136	Double blind, multiple dose, placebo controlled, randomized, two period crossover study. To investigate the potential PK and dynamic interaction between Pantoprazole and warfarin.
29726	Double blind, randomized placebo controlled, two period crossover study. To evaluate the possible influence of multiple doses of Pantoprazole on the PK/PD of warfarin.
296988	Open, two period repeated measurements design. To investigate a possible influence of Pantoprazole on the anticoagulant effect of phenprocoumon and its PK.
32019	Open, randomized two period crossover study. To evaluate the effect of repeated doses of Pantoprazole on the PK profile of a single dose of cisapride.
29689	Open, randomized, two period crossover, single dose study of Pantoprazole with antacid in healthy subjects. To assess the potential changes in serum Pantoprazole PK when an antacid is coadministered.
29725	Open, randomized, five period crossover, single oral dose of Pantoprazole or lansoprazole with diclofenac in healthy subjects. To assess potential interaction of Pantoprazole or lansoprazole on diclofenac PK.
32396	Single blind, two period randomized crossover study with an additional treatment (A). To investigate the PK/PD interaction between Pantoprazole and g;ibenclamide (glyburide). [Glucose and insulin levels were followed as dynamic markers.]
29722	Open, multiple oral dose study. To assess the effect of concomitant treatment with Pantoprazole on contraceptive activity of low dose oral contraceptive.

COMMENTS FOR IN-HOUSE

Rationale for drug and dosage

The sodium salt of Pantoprazole, as a sesquihydrate, was chosen for development due to its solid state stability relative to the free acid. Since Pantoprazole is unstable in aqueous solution, it is not possible to obtain a ready-to-use aqueous solution that will provide adequate shelf life.

The sponsor states that the efficacy of Pantoprazole in reduction of gastric acid secretion has been demonstrated repeatedly in the human studies included in this submission. The pharmacological action of Pantoprazole has facilitated rapid healing of the majority of duodenal ulcers, gastric ulcers, and GERD in clinical trials. Healing rates for duodenal ulcer during Pantoprazole therapy (40 mg/day) have been in the range of 92-100% by 4 weeks and have been significantly higher than the healing rates produced by the H2-receptor antagonist ranitidine. Similar doses of Pantoprazole healed approximately 97% of gastric ulcers within 8 weeks in clinical studies, a healing rate statistically superior to ranitidine. In US studies, Pantoprazole therapy was associated with healing of 74-88% of GERD at 8 weeks, a healing rate significantly better than ranitidine and at least comparable to omeprazole.

RECOMMENDATION/S

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, is of the opinion that NDA 20-987 can be filed.

However, the following comments should be communicated to the sponsor:

1. Assuming that Pantoprazole will be given concomitantly with antibiotics for the treatment of peptic ulcer disease as a result of *H. pylori* involvement, then some drug-drug interaction studies are warranted to asses the effect of the specific antibiotics on Pantoprazole and *vice-versa*. Initially, *in-vitro* studies should be conducted according to FDA's Industry Guidance "*Drug Metabolism/Drug Interaction Studies in Drug Development Process: Studies In Vitro*" (April 1997). Depending upon the findings of the *in-vitro* studies, *in-vivo* drug-drug interaction studies may be warranted.

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Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-180	NDA 20-988 (1x); DIV.FILE (1x); SANCHO (1X); WALSH (1X); LEED (1X)
HFD-870	JHUNT (1x); MLCHEN (1x)
HFD-850	SHUANG
CDR	Attn.: Barbara Murphy