Primary Review Issue

Is the —— tablet bioequivalent to the Phase III capsule of H 199/18 when administered under fasting conditions?

Study Design

Healthy male and female subjects (n = 36, age 20-50 years, BMI 19-27 kg/m^2) received 40 mg H 199/18 once daily dose of either a —— tablet (batch # H 1356-01-01-01) or a Phase III capsule (batch # H 1222-04-01-05) in an open, two-way crossover fashion separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of H 199/18 **before and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 7, 8, 10 and 12 hrs post-dose.**

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method —— (LOQ = — nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each formulation of H 199/18 using non-compartmental analysis: t_{max}, C_{max}, $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$.

Results

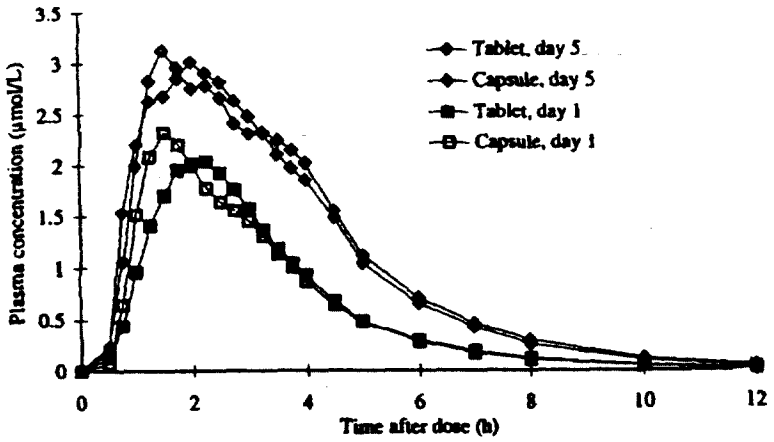

Figure 11:1 Mean plasma concentrations of H 199/18 following a single (day 1) and multiple (day 5) oral doses of different formulations of H 199/18 to healthy subjects (n=36). Values below LOQ are set to half the LOQ value.

Table 1. Estimates of the means of the primary PK parameters for H 199/18 after administration of 40 mg H 199/18 once daily dose as either Phase III capsule or —— tablet for 5 days

PK Parameter	40 mg × 1 Capsule	40 mg × 1 Tablet	Parameter Ratios (94% CI)
Day 1			
C_{max}	2.64	2.62	0.99 (0.85-1.15)
AUC_{0-t}	4.99	4.87	0.98 (0.88-1.08)
$AUC_{0-\infty}$	5.06	4.95	0.98 (0.88-1.08)
t_{max}	1.80	1.91	
$t_{1/2}$	1.01	1.00	
Day 5			
C_{max}	4.71	4.43	0.94 (0.86-1.03)
AUC_{0-t}	11.04	10.69	0.97 (0.89-1.05)
$AUC_{0-\infty}$	11.19	10.82	0.97 (0.89-1.05)
t_{max}	1.90	1.91	
$t_{1/2}$	1.32	1.29	

Reviewer's Comments

- *Based on estimated geometric means and confidence intervals of C_{max} and $AUC_{0-\infty}$, the —— 40 mg tablet and the Phase III capsule 40 mg formulation of H 199/18 are considered to be bioequivalent under fasting conditions.*

NDA: 21-153/ Study SH-QBE-0055 **Study Date: Mar-Jun 1999**

Type of Study: Bioequivalence of Clinical Trial and To-Be-Marketed Capsule Formulations Under fasting Conditions

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Study SH-QBE-0055 is entitled,

"A BIOEQUIVALENCE STUDY COMPARING H 199/18 MARKET CAPSULE, 40 mg, WITH THE H 199/18 PHASE III CAPSULE, 40 mg, FOLLOWING

SINGLE AND REPEATED ADMINISTRATION UNDER FASTING CONDITIONS IN HEALTHY MALE AND FEMALE SUBJECTS".

Objectives

To determine whether the market capsule and the phase III capsule of 40 mg H 199/18 are bioequivalent following single and repeated administration under fasting conditions.

Primary Review Issue

Are the TBM and clinical trial capsule formulations of H 199/18 bioequivalent, and hence interchangeable?

Study Design

Healthy male and female subjects (n = 37, age 20-50 years, BMI 19-27 kg/m^2) received 40 mg H 199/18 once daily dose of either the TBM capsule (batch # H 1222-06-01-05) or a Phase III capsule (batch # H 1222-04-01-05) for 5 days under fasting conditions in an open, two-way crossover fashion separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of H 199/18 **before and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 7, 8, 10 and 12 hrs post-dose**.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ——— (LOQ = — nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each formulation of H 199/18 using non-compartmental analysis: t_{max}, C_{max}, $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$.

Results

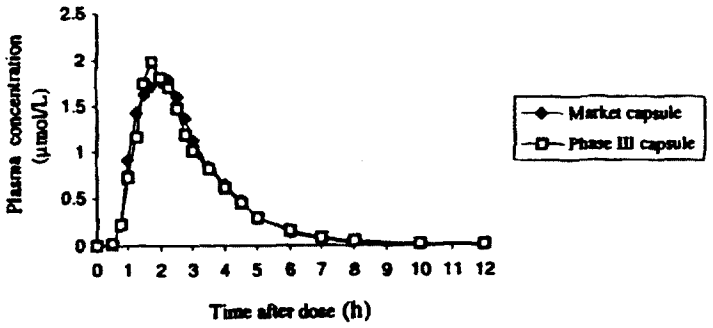

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Figure 11:1 Mean plasma concentrations following a single oral dose of 40 mg H 199/18 given as a market capsule or phase III capsule to healthy subjects (PP-analysis, n=37). Values below LOQ are set to half the LOQ value.

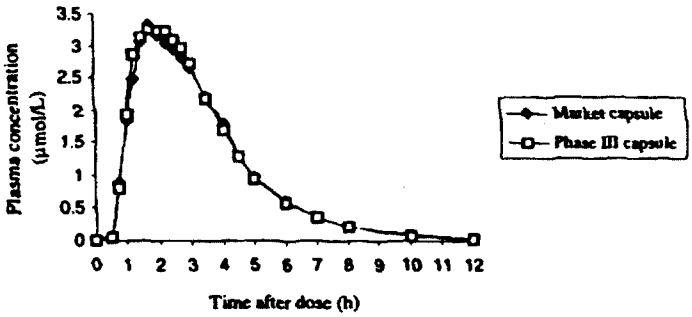

Figure 11:2 **Mean plasma concentrations of H 199/18 on day 5 following repeated administration of 40 mg H 199/18 given as a market capsule or phase III capsule to healthy subjects (PP-analysis, n=37). Values below LOQ are set to half the LOQ value.**

Table 1. Estimates of the means of the primary PK parameters for H 199/18 after administration of 40 mg H 199/18 once daily dose as either Phase III capsule or TBM capsule for 5 days

PK Parameter	Phase III Capsule	TBM Capsule	Parameter Ratios (94% CI)
Day 1			
C_{max}	2.41	2.64	1.09 (0.97-1.23)
AUC_{0-t}	4.14	4.29	1.04 (0.93-1.15)
$AUC_{0-\infty}$	4.21	4.35	1.03 (0.93-1.15)
t_{max}	1.97	1.96	
$t_{1/2}$	0.87	0.82	
Day 5			
C_{max}	4.57	4.55	0.99 (0.90-1.10)
AUC_{0-t}	11.07	10.98	0.99 (0.93-1.06)
$AUC_{0-\infty}$	11.19	11.09	0.99 (0.93-1.06)
t_{max}	1.81	1.83	
$t_{1/2}$	1.26	1.29	

Reviewer's Comments

- *Based on the estimated geometric means and confidence intervals of C_{max} and $AUC_{0-\infty}$, the TBM capsule 40 mg and the Phase III capsule 40 mg formulations of H 199/18 are considered to be bioequivalent under fasting conditions.*

NDA: 21-153/ Study SH-QBE-0056 **Study Date: Mar-Apr 1999**

Type of Study: **Bioequivalence of To-Be-Marketed Capsule and ——— Tablet Formulations Under Fed Conditions**

Study SH-QBE-0056 is entitled,

"A BIOEQUIVALENCE STUDY WITH A H 199/18 MARKET CAPSULE 40 mg WITH A NEW TABLET FORMULATION WITH A CAPSULE FORMULATION IN HEALTHY SUBJECTS".

Objectives

To determine whether a 40 mg ——— tablet formulation of H 199/18 is bioequivalent to the phase III capsule formulation under fed conditions during single and multiple dosing regimens.

Primary Review Issue

Is the ——— tablet bioequivalent to the Phase III capsule of H 199/18 when administered under fed conditions?

Study Design

Healthy male and female subjects (n = 76, age 20-50 years, BMI 19-27 kg/m^2) received 40 mg H 199/18 once daily dose of either a ——— tablet (batch # H 1356-01-01-01) or a Phase III capsule (batch # H 1222-04-01-05) under fed conditions in an open, two-way crossover fashion separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of H 199/18 before and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 14 and 16 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ——— (LOQ = — nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each formulation of H 199/18 using non-compartmental analysis: t_{max}, C_{max}, $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$.

Results

Table 1. Estimates of the means of the primary PK parameters for H 199/18 after administration of 40 mg H 199/18 once daily dose as either Phase III capsule or —— tablet for 5 days

PK Parameter	Phase III Capsule	—— Tablet	Parameter Ratios (94% CI)
Day 1			
C_{max}	1.05	1.30	1.24 (1.09-1.42)
AUC_{0-t}	2.43	3.09	1.27 (1.13-1.43)
$AUC_{0-\infty}$	2.83	3.60	1.27 (1.15-1.41)
Day 5			
C_{max}	2.24	2.89	1.29 (1.18-1.42)
AUC_{0-t}	6.83	9.47	1.39 (1.29-1.49)
$AUC_{0-\infty}$	6.94	9.58	1.38 (1.28-1.48)

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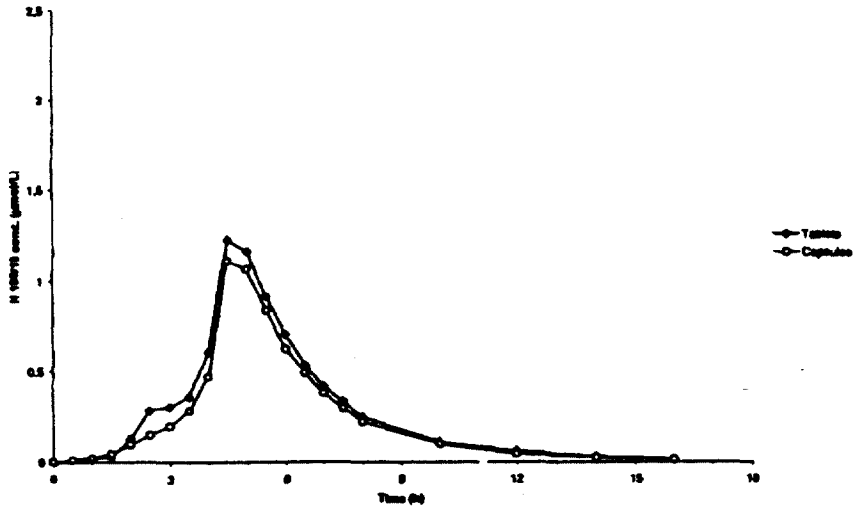

Figure 11:1 Mean plasma concentrations versus time profile for H 199/18 following a single oral dose of 40 mg (day 1) administered as a tablet (n = 76) or as a capsule (n = 76). Values below the LOQ are set to LOQ/2.

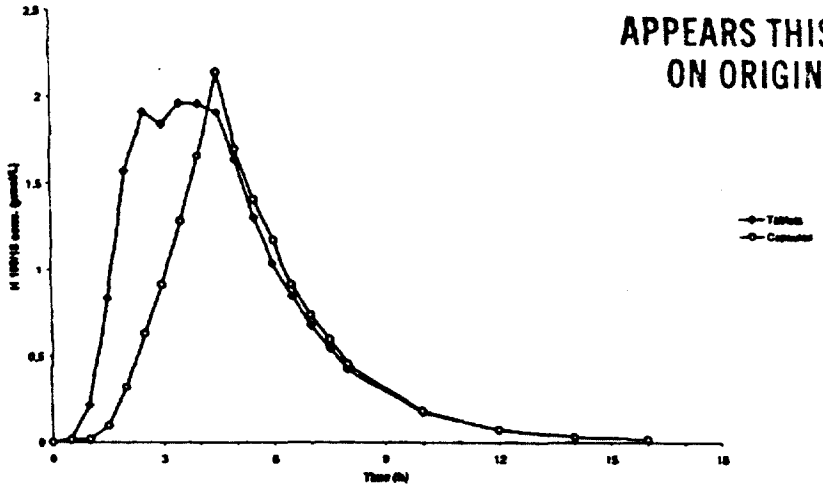

Figure 11:2 Mean plasma concentrations versus time profile for H 199/18 following repeated administration of 40 mg o.d. for five days (day 5) as a tablet (n =76) or as a capsule (n = 76). values below the loq are set to loq/2.

Reviewer's Comments

- *Based on the two-step bioequivalence approach employed by the sponsor, the [redacted] 40 mg tablet and the Phase III capsule 40 mg formulation of H 199/18 are considered to be bioequivalent under fed conditions.*

NDA: 21-153/ Study SH-QBE-0057 **Study Date: Mar-Jun 1999**

Type of Study: **Bioequivalence of To-Be-Marketed Capsule and Clinical Trial Capsule Formulations Under Fasting Conditions**

Study SH-QBE-0057 is entitled,

"A BIOEQUIVALENCE STUDY COMPARING A H 199/18 MARKET CAPSULE WITH THE H 199/18 PHASE III CAPSULE FOLLOWING SINGLE DOSE ADMINISTRATION UNDER FASTING CONDITIONS IN HEALTHY MALE ANF FEMALE SUBJECTS".

Objectives

To determine whether the market capsule and Phase II capsule of 20 mg H 199/18 are bioequivalent following single dose administration under fasting conditions.

Primary Review Issue

Is the TBM capsule bioequivalent to the Phase III capsule of 20 mg H 199/18 when administered under fasting conditions?

Study Design

Healthy male and female subjects (n = 76, age 20-50 years, BMI 19-27 kg/m^2) received a single 20 mg H 199/18 dose of either a TBM capsule (batch # H 1189-06-01-05) or a Phase III capsule (batch # H 1189-04-01-05) under fasting conditions in an open, two-way crossover fashion separated by a washout period of at least 6 days. In each treatment period, blood samples were drawn for determination of H 199/18 **before and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10 and 12 hrs post-dose.**

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ——— (LOQ = — nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each formulation of H 199/18 using non-compartmental analysis: t_{max}, C_{max}, $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$.

Results

Table 1. Estimates of the means of the primary PK parameters for H 199/18 after administration of 40 mg H 199/18 once daily dose as either Phase III capsule or ——— for 5 days

PK Parameter	TBM Capsule	Phase III Capsule	Parameter Ratios (94% CI)
C_{max}	1.09	0.98	1.12 (1.01-1.23)
AUC_{0-t}	1.57	1.49	1.06 (1.00-1.12)
$AUC_{0-\infty}$	1.64	1.56	1.05 (1.00-1.11)

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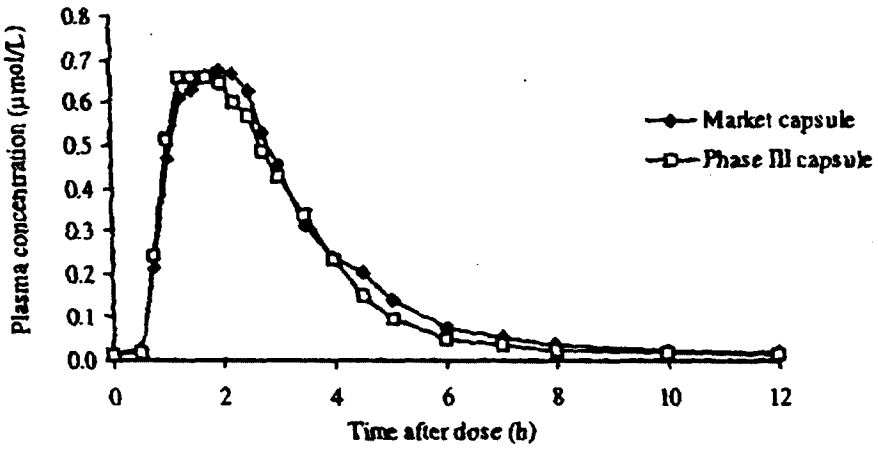

Figure 11:1 *Mean plasma concentrations of H 199/18 after single oral dose of H 199/18 market capsule 20 mg or phase III capsule 20 mg to healthy males and females (n=72) under fasting conditions.*

Reviewer's Comments

- *The 20 mg dose of the TBM capsule and Phase III capsule formulations of H 199/18 are deemed bioequivalent under fed conditions.*

NDA: 21-153/ Studies SH-QBE-0025 **Study Date: Oct-Dec 1997**

Type of Study: Food Effect on PK

Study SH-QBE-0025 is entitled,

"A FOOD INTERACTION STUDY ON H 199/18 CAPSULES IN HEALTHY MALE AND FEMALE SUBJECTS"

Objectives

- To compare the single-dose PK of H 199/18 when given as capsules together with food and under
fasting conditions.

- To compare the PK of H 199/18 and its main metabolites in healthy male and female subjects under fasting conditions.

Primary Review Issue

Is there a food effect on PK of H 199/18 ?

Study Design

Two single 40 mg daily capsules of H 199/18 were administered to 24 male and female subjects (12/12, age 20-50 years, BMI 19-27 kg/m^2) in a two-way crossover fashion separated by a washout period of at least 6 days. On each study day, H 199/18 was administered either immediately after food intake (standardized breakfast) or under fasting conditions. Blood samples were drawn before being assayed for H 199/18 and its major metabolites **before and at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, and 12 hrs post-dose**.

Analytical Assay

Plasma samples were analyzed according to methods ——— (for H 199/18 and the sulphone metabolite, LOQ = — nmol/L) and ——— (for the hydroxy metabolite, LOQ = — nmol/L), respectively.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for H 199/18 and its metabolites using non-compartmental analysis: t_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $t_{1/2}$.

Table 1. Estimated geometric means for H 199/18 under fasting conditions and after food intake following a single oral dose of 40 mg H 199/18 (n = 24)

	Geometric Mean
AUC	
Fasting	6.96
After Food	3.92
After Food/Fasting	0.56
C_{max}	
Fasting	3.70
After Food	1.17
After Food/Fasting	0.32
t_{max}	
Fasting	1.7
After Food	5.5

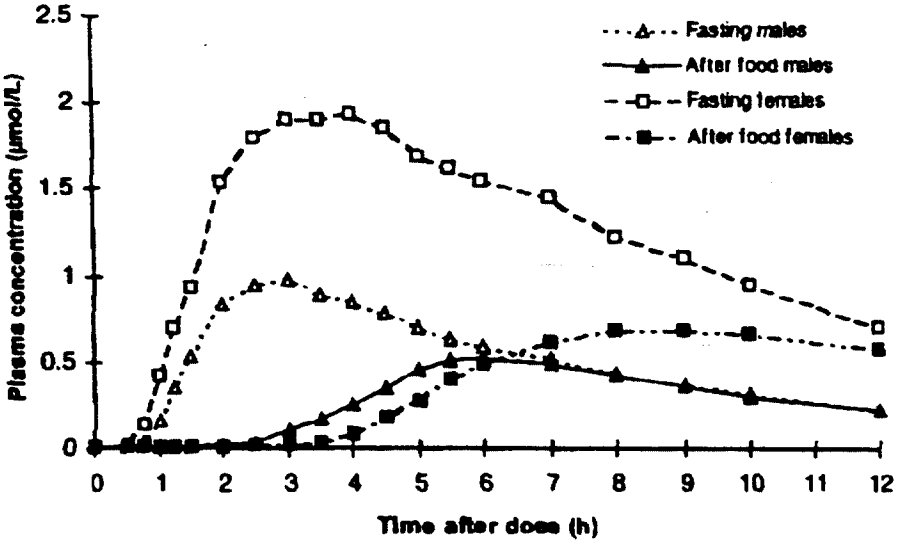

Fig. 1. Mean plasma concentration-time profile of H 199/18 after administration of 40 mg oral dose in both male and female subjects under fasting conditions and after food intake

Reviewer's Comments

- *Under fasting conditions, females had higher AUC and C_{max} values of H 199/18 and its sulphone metabolite when compared to males.*
- *Food intake resulted in a delayed and reduced absorption of H 199/18 in both male and female subjects. This, however, was more pronounced in females, where AUC and C_{max} decreased with food intake by 58% and 80%, respectively, while AUC and C_{max} in males decreased by 24% and 51%, respectively. Food seems to reduce oral bioavailability of H 199/18.*

NDA: 21-153/ Study SH-QBE-0030 **Study Date: Apr-Jun 1998**

Type of Study: Food Effect on PK

Study SH-QBE-0030 is entitled,

"A FOOD INTERACTION STUDY ON H 199/18 TABLETS IN HEALTHY MALE AND FEMALE SUBJECTS"

Objectives

- To compare the PK of the —— tablet formulation of H 199/18 when given together with food and under fasting conditions.
- To compare the PK of the —— tablet formulation of H 199/18 in male and female subjects and assess the safety and tolerability of H 199/18.

Primary Review Issue

Is there a food effect on PK of H 199/18?

Study Design

The 40 mg —— tablet of H 199/18 was administered once daily for 5 days to 23 male and female subjects (12/12, age 20-50 years, BMI 19-27 kg/m^2) in a two-way crossover fashion separated by a washout period of at least 13 days. On each treatment period, H 199/18 was administered either immediately after food intake (standardized breakfast) or under fasting conditions. Blood samples were drawn before being assayed for H 199/18 and its major **metabolites before and at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, and 12 hrs post-dose** on days 1 and 5 in each treatment period.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method —— (LOQ = — nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for H 199/18 using non-compartmental analysis: t_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $t_{1/2}$.

Results

Table 11:2 Geometric means of AUC (µmol·h/L), AUC_t (µmol·h/L) and C_{max} (µmol/L) for H 199/18 after food intake and during fasting conditions, and the ratio of the geometric means, following oral administration of H 199/18 —— tablet 40 mg o.m. on *study day 1* to healthy subjects. Estimates, limits for 95% CI and p-values for tests of equal geometric means are presented (n=24).

		Estimated geometric mean	95% confidence interval lower	upper	p-value
Day 1	AUC				
	After food	2.73	2.03	3.66	
	Fasting	4.07	3.03	5.46	
	After food/fasting	0.67	0.58	0.78	<0.001
	AUC_t				
	After food	2.60	1.95	3.47	
	Fasting	4.02	3.02	5.36	
	After food/fasting	0.65	0.55	0.76	<0.001
	C_{max}				
	After food	1.07	0.86	1.33	
	Fasting	2.44	1.97	3.03	
	After food/fasting	0.44	0.36	0.54	<0.001

Table 11:3 *Geometric means of* AUC (µmol·h/L), AUC_t (µmol·h/L) and C_{max} (µmol/L) for H 199/18 after food intake (n=24) and during fasting conditions (n=23), and the ratio of the geometric means, following oral administration of H 199/18 —— tablet 40 mg o.m. on *study day* 5 to healthy subjects. Estimates, limits for 95% CI and p-values for tests of equal geometric means are presented.

		Estimated geometric mean	95% confidence interval lower	upper	p-value
Day 5	AUC				
	After food	8.03	6.69	9.65	
	Fasting	10.79	8.95	12.99	
	After food/fasting	0.74	0.63	0.88	0.001
	AUC_t				
	After food	7.36	6.03	8.99	
	Fasting	10.70	8.73	13.11	
	After food/fasting	0.69	0.57	0.84	0.001
	C_{max}				
	After food	1.94	1.63	2.32	
	Fasting	4.17	3.48	5.00	
	After food/fasting	0.47	0.37	0.58	<0.001

- Food intake resulted in delayed and reduced absorption of H 199/18 after administration of 40 mg —— tablets.
- As noted earlier in study SH-QBE-0025, females had higher AUC and C_{max} values than males after administration of the H 199/18 —— tablets.

NDA: 21-153/ Study SH-QBE-0044 **Study Date: May-Jul 1998**

Type of Study: Food Effect on PK

Study SH-QBE-0044 is entitled,

"A FOOD INTERACTION STUDY REGARDING THE PHARMACOKINETICS AND EFFECT ON INTRAGASTRIC pH FOLLOWING TREAMENT WITH H 199/18 CAPSULES IN HEALTHY MALE AND FEMALE SUBJECTS"

Objectives

- To compare the PK and the effect on 24-hr intragastric pH of H 199/18 capsule 40 mg when given together with food and under fasting conditions on days 1 and 5.
- To compare the PK and the effect on 24-hr intragastric pH in males and females and to assess the safety and tolerability of H 199/18.

Primary Review Issue

Is there a food effect on PK of H 199/18?

Study Design

The 40 mg ——— of H 199/18 was administered once daily for 5 days to 23 male and female subjects (12/12, age 20-50 years, BMI 19-27 kg/m^2) in a two-way crossover fashion separated by a washout period of at least 13 days. On each treatment period,
H 199/18 was administered either immediately after food intake (standardized breakfast) or under fasting conditions. Blood samples were drawn before being assayed for H 199/18 and its major metabolites **before and at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 12 and 14 hrs post-dose** on days 1 and 5 in each treatment period.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ——— (LOQ = — nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for H 199/18 using non-compartmental analysis: t_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $t_{1/2}$.

Pharmacodynamics

The following PD markers were determined for each subject: The percentage of time with pH > 3 and > 4, and the median 24-hr pH.

Results

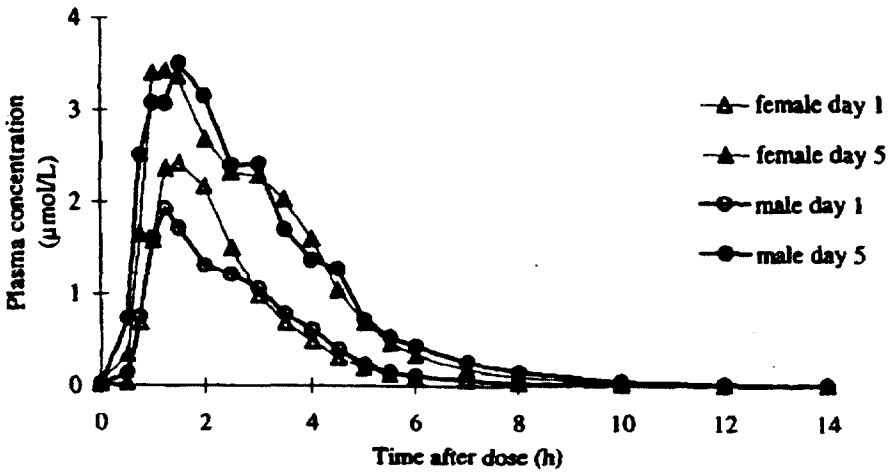

Figure 11:1 Mean plasma concentrations of H 199/18 under *fasting conditions* following daily oral doses of H 199/18 capsule 40 mg to healthy subjects.

Values below LOQ are set to half the LOQ value.

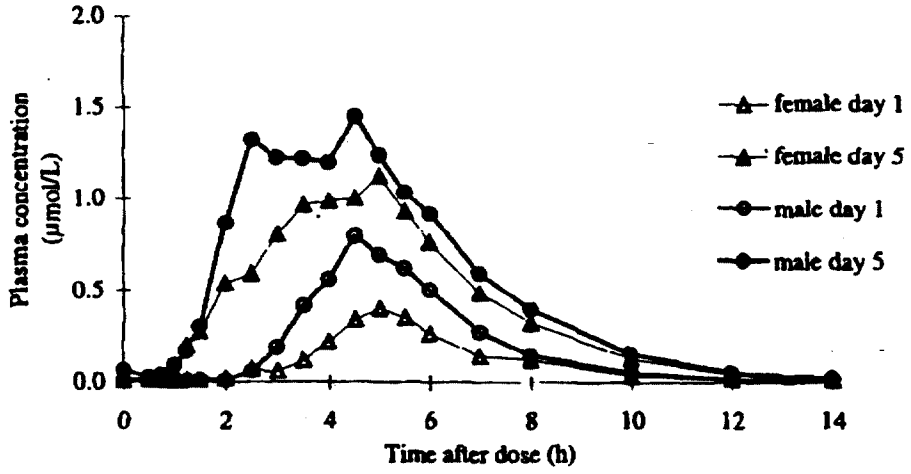

Figure 11:2 Mean plasma concentrations of H 199/18 after *food intake* following daily oral doses of H 199/18 capsule 40 mg to healthy subjects.

Table 11:5 **Means of percentage of time with pH>4 (%) and the difference of the means after food intake and under fasting conditions following daily oral doses of H 199/18 capsule 40 mg to healthy subjects. Estimates, limits for 95% CI and p-values for tests of equal means are presented (n=23).**

	Estimated mean	95% confidence interval lower	upper	p-value
Day 1				
After food	22.6	16.8	28.5	
Fasting	26.4	20.5	32.2	
After food-Fasting	-3.7	-10.6	3.1	0.27
Day 5				
After food	56.1	49.7	62.4	
Fasting	58.3	51.9	64.6	
After food-Fasting	-2.2	-8.5	4.1	0.48

Table 11:6 **Means of percentage of time with pH>4 (%) and the difference of the means under *fasting conditions* following daily oral doses of H 199/18 capsule 40 mg to *males* (n=12) and *females* (n=12). *Estimates, limits for* 95% CI and *p-values for* tests of equal means are presented.**

	Estimated mean	95% confidence interval lower	upper	p-value
Day 1				
Female	27.3	17.8	36.7	
Male	25.9	16.4	35.3	
Female-Male	1.4	-11.9	14.8	0.83
Day 5				
Female	55.1	46.0	64.3	
Male	62.4	53.2	71.6	
Female-Male	-7.2	-20.2	5.7	0.26

Table 11:7 **Means of percentage of time with pH>4 (%) and the difference of the means under *fed conditions following daily oral doses of H 199/18 capsule 40 mg to* males (n=12) and females (n=11). Estimates, limits for 95% CI and p-values for tests of equal means are presented.**

	Estimated mean	95% confidence interval lower	upper	p-value
Day 1				
Female	17.6	10.1	25.1	
Male	27.0	19.9	34.2	
Female-Male	-9.4	-19.8	0.9	0.073
Day 5				
Female	50.0	42.6	57.3	
Male	61.6	54.5	68.6	
Female-Male	-11.6	-21.7	-1.4	0.028

Table 1. Summary of the primary PK parameters after administration of 40 mg capsule of H 199/18 for 1 and 5 days in healthy male and female subjects

	Fasting State (Day 1)	Fed State (Day 1)	Fasting State (Day 5)	Fed State (Day 5)
AUC				
Female	4.59	1.40	9.97	5.03
Male	4.19	2.37	10.89	6.54
C_{max}				
Female	3.23	0.37	5.14	1.66
Male	2.56	0.86	4.38	1.95

Reviewer's Comments

- *In general, no major differences were observed between males and females with respect to the PK and PD of H 199/18. However, it was noted that the PK differences observed between males and females that received H 199/18 under the fed state on day 1 translated into clear differences in PD (% time with pH > 4).*
- *An identical study design was followed to study food-effect on PD (% time pH > 4) of H 199/18 ——— tablets 40 mg (Study SH-QBE-0050). The results indicate that no statistically significant differences exist in the effect on intragastric pH between fed and fasting conditions. On day 1, the estimated % time with pH > 4 was 38% under fed conditions and 33% under fasting conditions. On day 5, the estimated % time with pH > 4 was 61% under fed conditions and 56% under fasting conditions. However, it is noteworthy that the data for males and females were pooled, hence, any gender differences in PD could not be evaluated.*

NDA: 21-153/ Studies SH-QBE-0026 **Study Date: Feb-Sep 1998**

Type of Study: Influence of Hepatic Impairment on PK

Study SH-QBE-0026 is entitled,

"PHARMACOKINETICS OF H 199/18 AND ITS MAIN METABOLITES IN PATIENTS WITH VARYING DEGREES OF IMPAIRED LIVER FUNCTION"

Objectives

To study the pharmacokinetics of H 199/18 and its main metabolites after repeated dosing in patients with varying degrees of impaired liver function

Primary Review Issue

Is dosage adjustment of H 199/18 warranted in patients with liver impairment ?

Study Design

A single 40 mg daily capsule of H 199/18 was administered to 12 male and female patients (age 20-60 years, BMI 19-27 kg/m^2) for 5 days. Four patients were classified as having mild hepatic impairment (Child A), four as having moderate hepatic impairment (Child B) and four as having hepatic impairment (Child C). Blood samples were drawn before being assayed for H 199/18 and its major metabolites **before and at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12 and 24 hrs post-dose** on day 5.

Analytical Assay

Plasma concentrations of H 199/18 and its metabolites were determined according to method ——— LOQ was — nmol/L for H 199/18 and its sulphone metabolite, while the LOQ for the hydroxy metabolite was —nmol/L.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for H 199/18 and its metabolites using non-compartmental analysis: t_{max}, C_{max}, AUC_{0-t} and $t_{1/2}$. Descriptive statistics were calculated for the estimated PK parameters on day 1 and day 5. In addition, AUC and C_{max} on day 5 were compared to the corresponding parameters from a study with GERD patients (Study SH-QBE-0008) using a two-sample t-test.

Results

Table 1. Estimated geometric means of the primary PK parameters for H 199/18 on day 5 after administration of oral doses of 40 mg H 199/18 to GERD patients (SH-QBE-0008) or patients with hepatic impairment (n = 12)

PK Parameter	Group	Estimated Geomteric Mean
AUC_{0-t}	GERD	12.78
	Mild	18.17
	Moderate	22.55
	Severe	29.95
C_{max}	GERD	4.74
	Mild	6.53
	Moderate	5.41
	Severe	6.40
$t_{1/2}$	GERD	1.54
	Mild	1.28
	Moderate	2.36
	Severe	3.13

Reviewer's Comments

- *Plasma levels of H 199/18 in patients with mild and moderate hepatic impairment were generally higher but within the same range as that noted for GERD patients. However, patients with moderate and severe hepatic impairment showed markedly higher plasma levels of H 199/18 when compared to those of GERD patients, which suggests that dosage adjustment of H 199/18 may be warranted in patients with moderate and severe hepatic impairment.*

NDA: 21-153/ Studies SH-QBE-0037 **Study Date: Nov-Dec 1997**

Type of Study: Influence of Age and Gender on PK

Study SH-QBE-0037 is entitled,

"A PHARMACOKINETIC STUDY OF H 199/18 IN ELDERLY MALE AND FEMALE SUBJECTS"

Objectives

To study the pharmacokinetics of H 199/18 and its main metabolites in elderly male and female subjects

Primary Review Issue

Are age and gender important covariates that influence PK of H 199/18?

Study Design

A single 40 mg daily oral dose of H 199/18 was administered to 13 elderly male and female subjects (n = 6/7, age 70-80 years, weight 50-90 kg) for 5 days. Blood samples were drawn before being assayed for H 199/18 and its major metabolites before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12 and 24 hrs after dose administration on days 1 and 5.

Analytical Assay

Plasma concentrations of H 199/18 and its sulphone metabolite were determined according to method ——— (LOQ = —— mol/L), while those the hydroxy metabolite were determined according to method ——— LOQ = —— nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for H 199/18 using non-compartmental analysis: t_{max}, C_{max}, K_e, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2}$.

Descriptive statistics as well as 95% confidence intervals were calculated for the estimated PK parameters on day 1 and day 5. In addition, AUC and Cmax on day 5 were compared to the corresponding parameters from a study with gastroesophageal reflux disease (GERD) patients using a two-sample t-test.

Results

Table 1. estimated geometric means of
AUC (μmol·hr/L) of H 199/18 and its major metabolites

	Day 1	Day 5
H 199/18	8.25	15.98
Sulphone metabolite	10.77	27.36
Hydroxy metabolite	0.76	0.78

Table 2. estimated geometric means of C_{max} (μmol/L)
of H 199/18 and its major metabolites

	Day 1	Day 5
H 199/18	3.67	5.57
Sulphone metabolite	1.32	2.16
Hydroxy metabolite	0.28	0.21

- Estimated AUC and C_{max} values on both days 1 and 5 seem to be quite similar between elderly males and females.
- Consistent with results observed in earlier studies, AUC and C_{max} of H 199/18 are higher on day 5 compared to day 1, which points to time-dependent PK with multiple dose administration.
- Upon comparing results from the current study to those from a study in GERD patients (n = 36, age 45.2 years) on 40 mg daily H 199/18 for 5 days, it is notable that the estimated AUC and C_{max} values fall within the same range, which suggests that PK of H 199/18 is similar between healthy elderly subjects and the relevant patient population.

Reviewer's Comments

- *The gender effect on PK of H 199/18 noted earlier in study SH-QBE-0045 seems to be absent in the current study. It may be that the gender effect on PK was confounded by the age covariate since the study population was made up of elderly subjects.*
- *The AUC and C_{max} values for the sulphone metabolite, but not the hydroxy metabolite, increased in a manner parallel to H 199/18, which suggests that CYP 3A4, the primary metabolic enzyme(s) responsible for the formation of the sulphone metabolite, undergoes time-dependent changes, which may be related to the time-dependent changes in PK of H 199/18.*

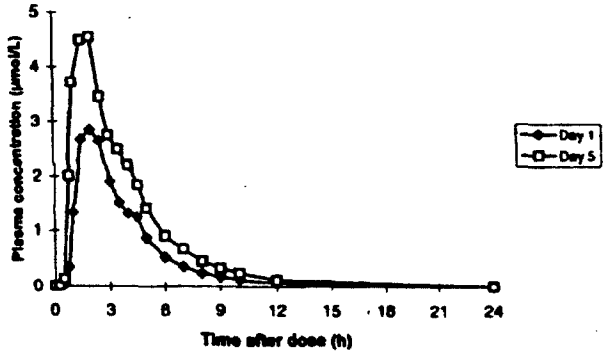

Figure 11:1Mean plasma concentrations of H 199/18 following oral doses of 40 mg of H 199/18 on day 1 (n=14) and on day 5 (n=13) to elderly subjects. Values below LOQ are set to half the LOQ value.

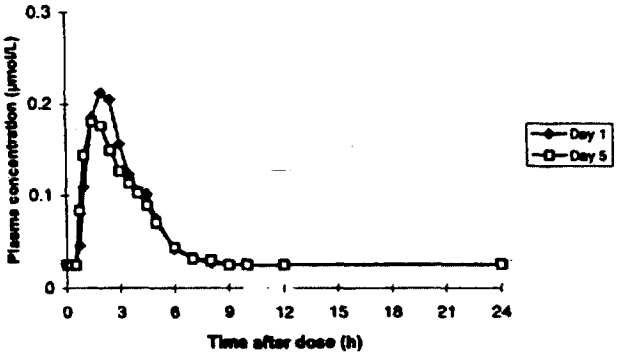

Figure 11:3 Mean plasma concentrations of the hydroxy metabolite following oral doses of 40 mg of H 199/18 on day 1 (n=14) and on day 5 (n=13) to elderly subjects. Values below LOQ are set to half the LOQ value.

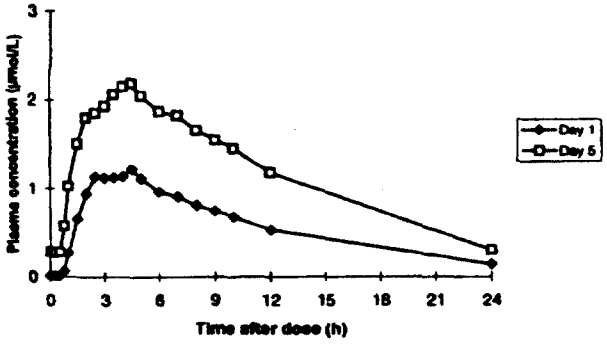

Figure 11:2 Mean plasma concentrations of the sulphone metabolite following oral doses of 40 mg of H 199/18 on day 1 (n=14) and on day 5 (n=13) to elderly subjects. Values below LOQ are set to half the LOQ value.

NDA: 21-153 Study Date: Sep 1999

Type of Study: Influence of Covariates on PK

The following report is entitled,

"EFFECT OF WEIGHT, AGE, GENDER and USE OF ORAL CONTRACEPTIVES ON AUC and C_{max} OF H 199/18"

Primary Review Issue

Does, weight, age, gender or the use of oral contraceptives influence PK of H 199/18?

Study Design

Several PK studies were utilized in the analysis where AUC and C_{max} values were calculated following oral administration of H 199/18 under fasting conditions. The effect of oral contraceptives was analyzed by analysis of variance (ANOVA), while linear regression was used to evaluate the effect of gender, age and weight.

Results

- **Concomitant Oral Contraceptives (OC)**: Only two studies included females with intake of OC. The analysis of AUC and C_{max} values from both studies shows no statistically significant effect of OC intake on PK.

Table 1. Estimated geometric means of AUC and C_{max} ratio of females with OC to females without OC

PK Parameter	Estimated Geometric Mean
AUC (Pills/No Pills)	1.45
C_{max} (Pills/No Pills)	1.15

- **Gender**: The analysis of AUC and C_{max} values from all studies that included females shows no statistically significant effect of gender intake on PK. However, albeit below statistical significance, the effect of gender is larger for single dosing relative to multiple dosing.

Table 2. Estimated geometric means of AUC and C_{max} ratio of females to males after single and multiple dosing

PK Parameter	Dosing Pattern	Estimated Geometric Mean
AUC (Females/males)	Single Dose	1.33
	Multiple Dose	1.13
C_{max} (Females/males)	Single Dose	1.27
	Multiple Dose	1.14

- **Age**: Based on the analyzed studies, an age increase of 20 years was estimated to give 6% and 15% higher C_{max} and AUC, respectively, after single dosing (5% and 10%, respectively, after multiple dosing), which are unlikely to be of clinical significance.

- **Weight**: As weight increases, AUC and C_{max} values seem to decrease. A weight increase of 10 kg was estimated to result in 12% and 5% decrease in AUC after single and multiple dosing, respectively. In a similar manner, C_{max} decreases by 15% and 8% after single and multiple dosing, respectively.

Reviewer's Comments

- *None of the covariates evaluated (concomitant OC administration, gender, weight and age) seemed to influence the PK of H 199/18 to an extent sufficiently large to raise any major concerns due to the relatively wide safety margin of H 199/18.*

NDA: 21-153/ Study 24312 **Study Date: Nov 1998**

Type of Study: Identification of *In Vitro* Metabolic Enzymes

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Study 24312 is entitled,

"EFFECTS OF H 199/18 ON CYTOCHROME P450 ISOFORM-SELECTIVE ACTIVITIES".

Objectives

To evaluate the potential for H 199/18 to inhibit the metabolism of other co-administered drugs.

Primary Review Issue

How likely is it that H199/18 will inhibit the metabolism of co-administered drugs ?

Study Design

An initial study was conducted to test for inhibition of each CYP isoform-selective activity *in vitro* by H 199/18 at 10 or 50 μM. These two concentrations are in the range of K_m values and relevant inhibitor concentrations for many drugs. The substrate concentration was equal to K_m of the substrate used for each CYP isoform, which makes it possible to calculate an apparent K_i value. For those enzyme activities that were inhibited by more than 30% in the initial inhibition study, the IC_{50} and/or K_i was determined. The incubations were done at 37°C. Control incubations contained the specific substrate but no test compound. To check whether the test compound or its metabolites interfered with the analysis of each CYP activity assay, samples containing the test compound, microsomes and NADPH, but no substrate, were incubated. All experiments were done in triplicate. In separate experiments, known specific inhibitors of each selective CYP isoform were incubated to establish that the microsomes were suitable for the study of the inhibitory potential of H 199/18.

Results and Conclusions

Table 1. K_i values for in vitro inhibition of specific CYP isoforms by H 199/18

CYP isoform	K_i (μM)
CYP 1A2	—
CYP 2A6	—
CYP 2C9	—
CYP 2D6	84
CYP 2E1	58
CYP 3A4	—

The potential for H 199/18 to inhibit human liver microsomal CYP enzymes was ranked as follows:

CYP 2C9 > CYP 3A4= CYP 1A2 > CYP 2E1 > CYP 2D6 > CYP 2A6

Reviewer's Comments

- *The maximal plasma concentration observed in vivo with the highest proposed H 199/18 dosage (40 mg) after single or multiple dose administration is around 5 μM, which falls significantly below the K_i values for in vitro inhibition of all CYP isoforms by H 199/18 except for CYP 2C9 and CYP 3A4. This suggests that at therapeutic drug levels, H 199/18 is likely to inhibit to an appreciable extent CYP isozymes 2C9 and 3A4.*

- *The effect of H 199/18 on CYP 2C19 could not be assessed in the study due to interference with analytical detection. However, based on earlier in vivo studies, H 199/18 is known to have significant CYP 2C19 inhibitory activity.*

NDA: 21-153/ Study SH-QBE-0003 **Study Date: Apr-Jun 1995**

Type of Study: *In Vivo* Drug-Drug Interaction Study With Diazepam

Study SH-QBE-0003 is entitled,

"PHARMACOKINETICS OF DIAZEPAM WITH AND WITHOUT CO-ADMINISTRATION OF H 199/18 IN HEALTHY VOLUNTEERS".

Objectives

To investigate the PK of diazepam and the formation of one of its active metabolites, N-desmethyldiazepam, during repeated oral administration H 199/18 in healthy subjects.

Primary Review Issue

Is dose adjustment warranted upon concomitant administration of diazepam with H 199/18?

Study Design

Either 30 mg H 199/18 solution or placebo was administered once daily for 9 days to 10 male subjects (age 20-40 years, weight 66-90 kg) in a double-blind, two-way crossover fashion separated by a washout period of at least 14 days. On day 5, a single dose of 0.1 mg/kg diazepam was administered as a short-term IV infusion. Blood samples were drawn at 15, 30, 45, 69, 120, 180, 240 and 360 min following administration of H 199/18 or placebo. For determination of diazepam and N-desmethyldiazepam, blood samples were drawn at 5, 10, 20 and 30 min and 1, 2, 4, 6, 8, 10, 12, 24, 36, 48 72, 96 and 120 hrs
Following diazepam dose administration.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ——— (LOQ = — nmol/L). For determination of diazepam and N-desmethyldiazepam, method ——— was utilized.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for H 199/18, diazepam and N-desmethyldiazepam using non-compartmental analysis: t_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $t_{1/2}$.

Results

Table 4. Pharmacokinetic estimates (AUC, CL and $t_{1/2}$) and 95% confidence intervals of diazepam during treatment with H 199/18 or placebo in healthy subjects.

Variable	Effect	Estimate	Lower	Upper
$AUC_{0-\infty}$ (µmol*h/L)	H 199/18	35.88*	28.67	44.90
	Placebo	19.83	15.85	24.81
CL (L/h)	H 199/18	0.71*	0.55	0.91
	Placebo	1.28	1.00	1.64
$t_{1/2}$ (h)	H 199/18	85.80	53.61	117.99
	Placebo	43.10	10.91	75.29

*= p-value= 0.002 compared with placebo.

Table 5. Pharmacokinetic estimates (AUC and C_{max}) and 95% confidence intervals of N-desmethyldiazepam during treatment with H 199/18 or placebo in healthy subjects.

Variable	Effect	Estimate	Lower	Upper
AUC_{0-t} (µmol*h/L)	H 199/18	10.53*	8.61	12.88
	Placebo	12.65	10.35	15.47
C_{max} (µmol/L)	H 199/18	0.12	0.10	0.15
	Placebo	0.14	0.11	0.17

*= p-value= 0.03 compared with placebo.

Table 6. Pharmacokinetic estimates (AUC, C_{max} and $t_{1/2}$) and 95% confidence intervals of H 199/18 during repeated treatment with H 199/18 on days 1 and 5 in healthy subjects.

Variable	Effect	Estimate	Lower	Upper
$AUC_{0-\infty}$ (µmol*h/L)	Day 1	3.38	2.40	4.76
	Day 5*	7.91	5.62	11.13
C_{max} (µmol/L)	Day 1	2.97	2.70	3.27
	Day 5**	4.31	3.91	4.74
$t_{1/2}$ (h)	Day 1	0.88	0.65	1.12
	Day 5*	1.27	1.03	1.50

*= p-value <0.0001 compared with day 1.
**= p-value= 0.0002 compared with day 1

Reviewer's Comments

- *The AUC and C_{max} values of diazepam were higher after 5 days of co-administration with H 199/18, which indicates an inhibition of diazepam clearance by H 199/18, likely via inhibition of CYP-450 metabolic enzymes. Since diazepam is a substrate of CYP 2C and CYP 3A4 enzymes, it would be expected that its metabolism would be inhibited to some extent by H 199/18.*

- *It is not clear why the sponsor conducted the study using an H 199/18 dose (30 mg) that is lower than the maximum proposed dose (40 mg). In any case, while the current study showed an increase in diazepam AUC by 45% with a 30 mg dose of H 199/18, another study that evaluated the interaction potential for the 40 mg dose of omeprazole showed an increase in diazepam AUC by 142%[1]. In addition, a latter study showed that omeprazole 20 mg increased diazepam AUC by 47% in slow metabolizers and 70% in rapid metabolizers.*

NDA: 21-153/ Study SH-QBE-0004 **Study Date: May-Jun 1995**

Type of Study: *In Vivo* Drug-Drug Interaction Study With Phenytoin

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Study SH-QBE-0004 is entitled,

"PHARMACOKINETICS OF PHENYTOIN WITH AND WITHOUT CO-ADMINISTRATION OF H 199/18 SODIUM IN HEALTHY VOLUNTEERS".

Objectives

To investigate the PK of phenytoin during repeated oral administration H 199/18 in healthy subjects.

Primary Review Issue

Is dose adjustment warranted upon concomitant administration of phenytoin with H 199/18?

Study Design

Either 30 mg H 199/18 solution or placebo was administered once daily for 7 days to 17 male subjects (age 20-40 years, weight 66-90 kg) in a double-blind, two-way crossover fashion separated by a washout period of at least 14 days. On day 5, a single dose of 300 mg phenytoin was administered orally. Blood samples were drawn at 15, 30, 45, 69, 120, 180, 240 and 360 min following administration of H 199/18 or placebo. For

[1] Andersson T. *Drug interactions with omeprazole.* Clin. Pharmacokin. (1991), 21:195-212.

determination of phenytoin, blood samples were drawn at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72 hrs following phenytoin dose administration.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ——— LOQ = — nmol/L). For determination of phenytoin, analytical method ——— was utilized.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for H 199/18 and phenytoin using non-compartmental analysis: t_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $t_{1/2}$.

Results

- The AUC of phenytoin increased by 11% during treatment with H 199/18 compared to placebo, while C_{max} was unchanged.

Reviewer's Comments

- *The interaction of phenytoin with H 199/18 is unlikely to be of any clinical significance.*
- *An earlier study that was conducted to evaluate the potential interaction between H 199/18 and phenytoin in healthy male and female subjects showed that the AUC and C_{max} of phenytoin increased by 13% and 10%, respectively, which corroborates the results of the current study (Study SH-QBE-0032).*
- *An additional placebo-controlled, parallel-group study was conducted in 24 epileptic patients already on phenytoin to evaluate the drug interaction potential of concomitant daily doses of 40 mg H 199/18 capsules over a period of 2 weeks. The results showed an increase of 13% in the mean steady-state trough serum levels of phenytoin, which is not of any significant clinical relevance (Protocol no. 201).*

NDA: 21-153/ Study SH-QBE-0005 **Study Date: Apr-Jun 1995**

Type of Study: *In Vivo* Drug-Drug Interaction Study With Quinidine

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Study SH-QBE-0003 is entitled,

"PHARMACOKINETICS OF QUINIDINE WITH AND WITHOUT CO-ADMINISTRATION OF H 199/18 SODIUM IN HEALTHY VOLUNTEERS".

Objectives

To investigate the PK of quinidine and the formation of one of its active metabolites, 3-hydroxyquinidine, during repeated oral administration H 199/18 in healthy subjects.

Primary Review Issue

Is dose adjustment warranted upon concomitant administration of quinidine with H 199/18 ?

Study Design

Either 30 mg H 199/18 solution or placebo was administered once daily for 6 days to 12 healthy male subjects (age 20-40 years, weight 66-90 kg) in a double-blind, two-way crossover fashion separated by a washout period of at least 14 days. On day 5, a single oral dose of 400 mg quinidine was administered. Blood samples were drawn at 15, 30, 45, 69, 120, 180, 240 and 360 min following administration of H 199/18 or placebo. For determination of quinidine and 3-hydroxyquinidine, blood samples were drawn at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hrs following administration of the quinidine dose

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ——— (LOQ = — nmol/L). For determination of quinidine and 3-hydroxyquinidine, analytical method ——— was utilized.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for H 199/18, quinidine and 3-hydroxyquinidine using non-compartmental analysis: t_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $t_{1/2}$.

Results

Table 1. Summary of the estimated AUC values for quinidine and 3-OH-quinidine after concomitant administration of either H 199/18 (30 mg) or placebo

	Quinidine	3-OH-Quinidine
H 199/18	60.1	10.2
Placebo	52.7	10.0

Reviewer's Comments

- *The concomitant administration of H 199/18 with quinidine does not seem to significantly affect the PK of either quinidine or 3-OH-quinidine. Hence, the H 199/18-quinidine interaction is not expected to be of any clinical relevance.*

NDA: 21-153/ Study SH-QBE-0034 Study Date: Dec 1997-Mar 1998

Type of Study: *In Vivo* Drug-Drug Interaction Study With Amoxicillin and Clarithromycin

Study SH-QBE-0034 is entitled,

"AN INTERACTION STUDY BETWEEN H 199/18, AMOXICILLIN AND CLARITHROMYCIN IN HEALTHY MALE AND FEMALE SUBJECTS".

Objectives

To investigate the potential PK interactions between a 40 mg H 199/18 capsule once daily, 1 g amoxicllin b.i.d. and 500 mg clarithromycin b.i.d. after repeated administration in healthy subjects.

Primary Review Issue

Is dose adjustment warranted upon concomitant administration of clarothromycin and amoxicillin with H 199/18 ?

Study Design

Each of 17 male and female subjects (age 20-50 years, BMI 19-27 kg/m^2) received a 40 mg H 199/18 capsule once daily, 1 g amoxicllin b.i.d., 500 mg clarithromycin b.i.d. or the triple combination orally for 7 days in an open-label, four-way crossover fashion separated by a washout period of 14-28 days. For determination of H 199/18, amoxicillin, clarithromycin and 14-OH-clarithromycin, blood samples were drawn on day 7 of each treatment period before and at 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10 and 12 hrs after dose administration. In addition, morning and evening blood samples were drawn on days 5 and 6 to insure that steady state was reached.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ——— (LOQ = — nmol/L). For determination of amoxicillin, method ——— (LOQ = — nmol/L)was utilized. Plasma concentrations of clarithromycin and 14-OH-clarithromycin were determined using method ——— (LOQ = —nmol/L and —nmol/L, respectively).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for H 199/18, amoxicillin, clarithromycin and 14-OH-clarithromycin using non-compartmental analysis: t_{max}, C_{max}, $AUC_{0-\tau}$ and $t_{1/2}$.

Results

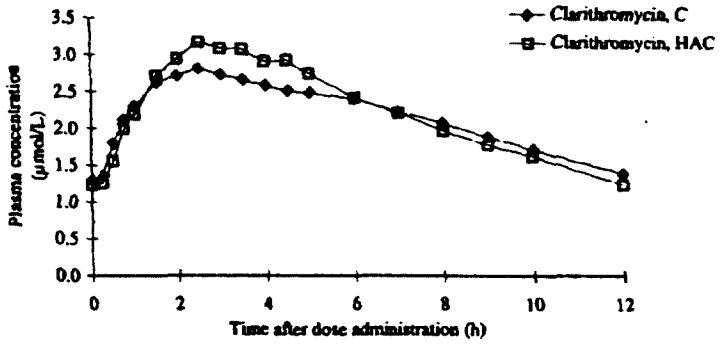

Figure 11:3 Mean plasma concentrations of clarithromycin on day 7 following oral administration of clarithromycin 500 mg b.i.d. (C) and in combination (HAC) with H 199/18 40 mg o.m.and amoxicillin 1 g b.i.d. (n=18).

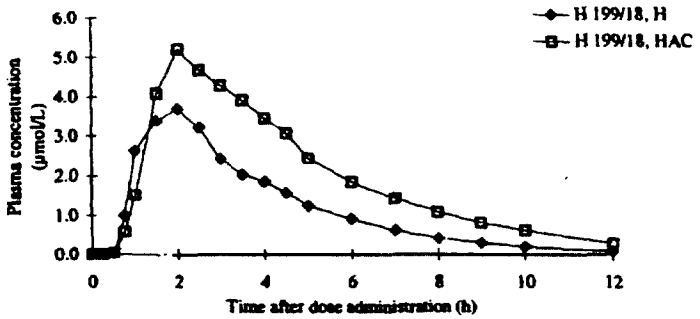

Figure 11:1 Mean plasma concentrations of H 199/18 on day 7 following oral administration of H 199/18 40 mg o.m.(H) and in combination (HAC) with amoxicillin 1 g b.i.d. and clarithromycin 500 mg b.i.d. (n=18). Values below LOQ are set to LOQ/2 in the graphs.

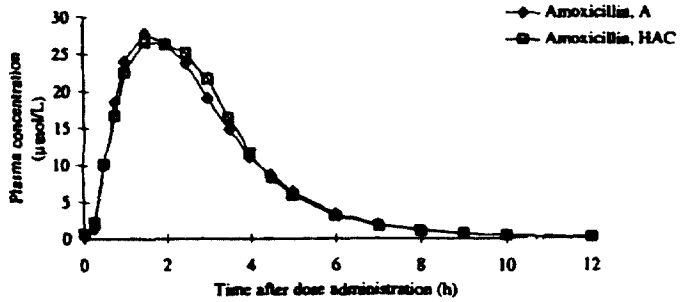

Figure 11:2 Mean plasma concentrations of amoxicillin on day 7 following oral administration of amoxicillin 1 g b.i.d.(A) and in combination (HAC) with H 199/18 40 mg o.m.and clarithromycin 500 mg b.i.d. (n=19). Values below LOQ are set to LOQ/2 in the graphs.

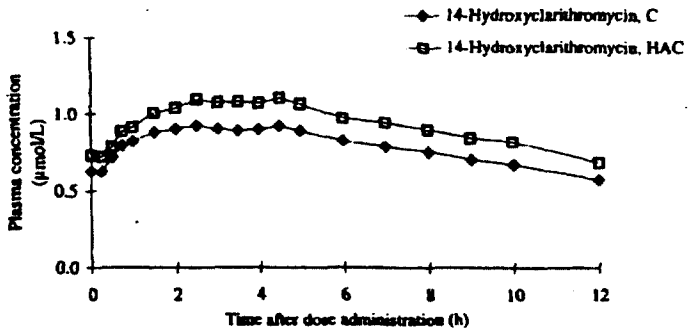

Figure 11:4 Mean plasma concentrations of 14-hydroxyclarithromycin on day 7 following oral administration of clarithromycin 500 mg b.i.d. (C) and in combination (HAC) with H 199/18 40 mg o.m.and amoxicillin 1 g b.i.d. (n=18).

- The PK of both amoxicillin and clarithromycin after combination treatment were very similar to those of monotherapies. However, the AUC and C_{max} of 14-OH-clarithromycin were 19% and 22% higher, respectively, with combination treatment compared to monotherapy. As for H 199/18, AUC, C_{max} and $t_{1/2}$ were 70%, 18% and 35% higher, respectively after combination treatment.

Table 11:2 Geometric means of AUC_τ (µmol·h/L), C_{max} (µmol/L) and $t_{1/2}$ (h) of H 199/18 and the ratio of the geometric means following repeated oral administration of 40 mg H 199/18 o.m.or a triple combination (H 199/18 40 mg o.m., amoxicillin 1 g b.i.d. and clarithromycin 500 mg b.i.d.) to healthy subjects. Estimates, limits for 95% CI and p-values for tests of equal geometric means (n=18) are presented.

	Estimated geometric mean	95% confidence interval lower	upper	p-value
AUC_τ				
H 199/18 (H)	13.31	11.12	15.95	
Triple combination (HAC)	22.69	18.94	27.17	
HAC /H	1.70	1.40	2.08	<0.001
C_{max}				
H 199/18 (H)	4.94	4.29	5.69	
Triple combination (HAC)	5.84	5.07	6.73	
HAC/H	1.18	1.00	1.40	0.050
$t_{1/2}$				
H 199/18 (H)	1.55	1.37	1.76	
Triple combination (HAC)	2.10	1.85	2.38	
HAC/H	1.35	1.19	1.54	<0.001

Reviewer's Comments

- *In general, no clinically significant changes were observed in the PK of clarithromycin, 14-OH-clarithromycin or amoxicillin. As for H 199/18, a significant increase in exposure was noted with the combination treatment, which is likely due to the inhibitory effect exerted by clarithromycin on CYP 450 metabolic enzymes.*

- *An additional study was conducted that evaluated the potential PK interactions of amoxicillin 1 g b.i.d. and clarithromycin 500 mg b.i.d. with a 20 mg b.i.d. regimen of H 199/18 in healthy subjects. The study showed that whereas the PK of clarithromycin and amoxicillin changed little with combination treatment compared to monotherapy, AUC, C_{max} and $t_{1/2}$ of H 199/18 increased by 127%, 39% and 50%, respectively (Study SH-QBE-0040). An average increase in AUC of H 199/18 by 100% with concomitant clarithromycin treatment might warrant dose adjustment.*

NDA: 21-153/ Study SH-QBE-0036 **Study Date: Feb-Apr 1998**

Type of Study: *In Vivo* Drug-Drug Interaction Study With Cisapride

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Study SH-QBE-0036 is entitled,

"AN INTERACTION BETWEEN H 199/18 AND CISAPRIDE IN HEALTHY MALE AND FEMALE SUBJECTS".

Objectives

To investigate potential PK interactions between H 199/18 and cisapride during repeated oral administration in healthy subjects.

Primary Review Issue

Is dose adjustment warranted upon concomitant administration of cisapride with H 199/18 ?

Study Design

Nineteen male and female subjects (age 20-50 years, BMI 19-27 kg/m^2) received a 40 mg H 199/18 capsule once daily or 10 mg cisapride tablet b.i.d. or a combination of the two for 7 days to in a double-blind, three-way crossover fashion separated by a washout period of at least 14 days. In each treatment period, blood samples were drawn for determination of H 199/18 and cisapride **before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 18 and 24 hrs post-dose**.

Analytical Assay

Plasma samples were analyzed for H 199/18 according to method ——— (LOQ = — nmol/L). For determination of cisapride, method —— LOQ = — nmol/L) was utilized.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for H 199/18 and cisapride using non-compartmental analysis: t_{max}, C_{max}, $AUC_{0-\tau}$ and $t_{1/2}$.

Results

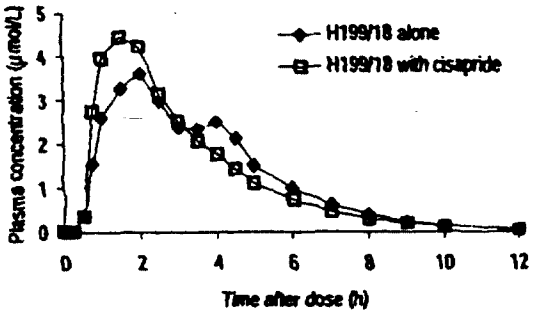

Figure 11:1 **Mean plasma concentrations of H 199/18 following oral administration of H 199/18 capsule 40 mg o.m. alone and in combination with cisapride tablet 20 mg b.i.d. for seven days. Plasma concentration values below LOQ have been replaced by LOQ/2 (n=23).**

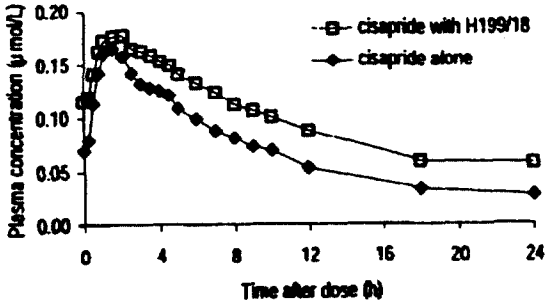

Figure 11:2 **Mean plasma concentrations of cisapride following oral administration of cisapride tablet 20 mg b.i.d. alone and in combination with H 199/18 capsule 40 mg o.m. for seven days. Plasma concentration values below LOQ have been replaced by LOQ/2 (n=22).**

Reviewer's Comments

- *The PK of H 199/18 does not seem to be influenced significantly by cisapride. On the other hand, the AUC and $t_{1/2}$ for cisapride were 32% and 31% larger, respectively, after co-administration with H 199/18 compared to cisapride alone. The clinical relevance of such an increase in cisapride plasma levels is not clear. In any case, the US marketing of cisapride has been discontinued, hence the potential cisapride-H 199/18 interaction of no concern.*

NDA: 21-153/ Study SH-QBE-0038 **Study Date: Jan-Jun 1998**

Type of Study: *In Vivo* Drug-Drug Interaction Study With Warfarin

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Study SH-QBE-0038 is entitled,

"AN INTERACTION STUDY BETWEEN H 199/18 AND WARFARIN IN WARFARIN-TREATED PATIENTS".

Objectives

- To determine the effect of H 199/18 on the steady-state plasma levels and anticoagulant effect of warfarin in patients on warfarin.

Primary Review Issue

Is dose adjustment warranted upon concomitant administration of warfarin with H 199/18?

Study Design

Thirty male and female subjects (age 20-70 years, BMI 19-35 kg/m^2) received a 40 mg H 199/18 capsule or a placebo capsule once daily for 3 weeks in a double-blind, two-way crossover fashion. Blood samples were drawn for determination of the R- and S- warfarin enantiomers at the following time points:

Weeks 1-2 (Run-in): Samples taken in the morning of the first day of each week

Weeks 3-5 (Treatment period I): Samples taken in the morning of the first day of each week and in the morning of the last two days in week 5

Weeks 6-8 (Treatment period II): Samples taken in the morning of the first day in weeks 7 and 8 and in the morning of the last two days in week 8

Weeks 9-11 (Follow-up): Samples taken in the morning of the last in each week

Analytical Assay

Plasma samples were analyzed for the R- and S- enantiomers of warfarin according to method ——— (LOQ = ——— nmol/L for both enantiomers).

Pharmacokinetics & Pharmacodynamics

The primary pharmacokinetic parameter estimated for the two warfarin enantiomers was the trough plasma concentrations, while the primary pharmacodynamic parameter determined was the coagulation activity expressed as coagulation time in seconds.

Results

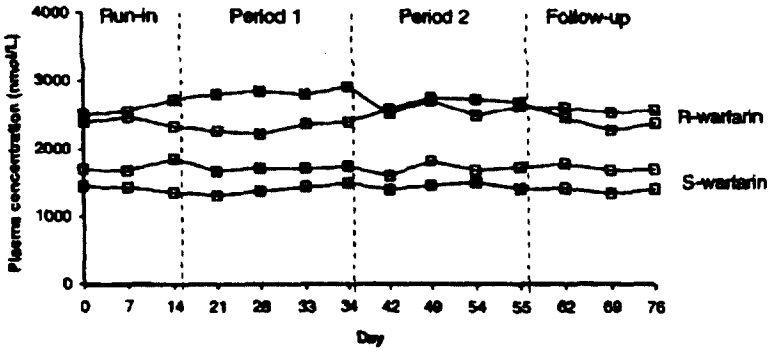

Figure 11:1 Trough plasma concentrations of R- and S-warfarin (nmol/L) during repeated administration of 40mg H 199/18 (•) and placebo (○) in visit sequence. Each data point in each sequence represents the mean of 13 patients.

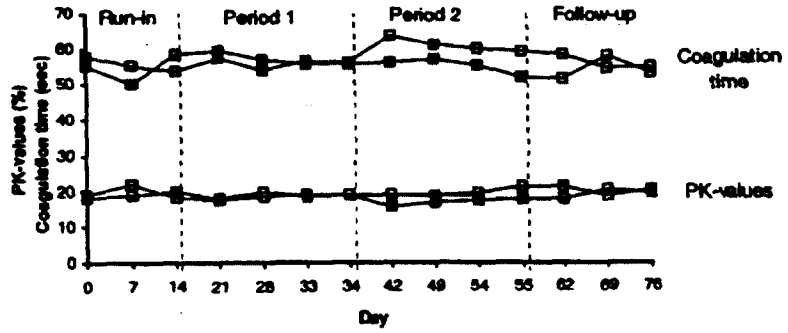

Figure 11:2 Blood coagulation values, PK (%) and blood coagulation times, PT (s) during repeated administration of 40mg H 199/18 (•) and placebo (○) in visit sequence. Each data point in each sequence represents the mean of 13 patients.

- The mean trough plasma concentration of R-warfarin was increased by 13% during H 199/18 treatment compared to placebo, while that of S-warfarin was unchanged.

Reviewer's Comments

The changes observed in the trough plasma levels of the two enantiomers of warfarin during H 199/18 treatment were of no clinical relevance.

NDA: 21-153/ Study 24312 **Study Date: Apr 1997**

Type of Study: *In Vivo* Drug-Drug Interaction Study With Caffeine

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Study 24312 is entitled,

"PHARMACOKINETICS AND INFLUENCE ON CAFFEINE METABOLISM OF H 199/18 SODIUM COMPARED TO OMEPRAZOLE SODIUM IN HEALTHY SUBJECTS".

Objectives

1. To evaluate the potential for H 199/18 to inhibit the metabolism of caffeine (CYP 1A2 substrate).
2. To evaluate the pharmacokinetics and effect on pentagastrin stimulated gastric acid secretion of H 199/18 and H 199/19 compared to omeprazole following repeated administration of 15 mg doses of each compound to rapid metabolizers of omeprazole.

Primary Review Issue

- **Is there a metabolic drug-drug interaction between H 199/18 and caffeine?**
- **What are the pharmacokinetic and pharmacodynamic characteristics after administration of 15 mg doses of each of omeprazole, H 199/18 and H 199/19?**

Study Design

Open, randomized, three-way, crossover study in healthy subjects

Subjects	9 subjects; 5 slow metabolizers and 4 rapid metabolizers of omeprazole (phenotype determined using the S/R mephenytoin test[1])
Key Inclusion Criteria	Age 20-50 yrs, wt within 66-86 kg
Treatments	Subjects were randomized to receive aqueous solns of each of H 199/18, H 199/19 and omeprazole once daily over 7 days (slow metabolizers received **60 mg** doses of each compound, while rapid metabolizers received **15 mg** doses). To avoid degradation of the acid labile compounds in the acidic environment of the stomach, 50 ml of a buffer soln ($NaHCO_3$ soln, pH 9.0) was given to each

[1] Sanz et al. *S-mephenytoin hydroxylation phenotypes in a swedish population determined after coadministration with debrisoquin.* Clin Pharmacol Ther. 1989; 45:495-499.

subject 5 min prior to and 10, 20 and 30 min after dose administration. All slow metabolizing subjects received a concomitant daily dose of ^{13}C-[N-3-methyl]-caffeine over the same period.

Washout Period 14 days

Plasma Sampling 5 ml plasma samples were collected for determination of each compound and its metabolites at the following time points on days 1 and 7 of each treatment period:

a) **Slow metabolizers**: At –5, 0 (predose), 10, 15, 20, 30, and 45 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 and 12 hrs after dose administration

b) **Rapid metabolizers**: At –5, 0 (predose), 10, 15, 20, 30, and 45 min, 1, 1.5, 2, 3, 4, 5.5, 5.75, 6, 6.25, 6.5, 6.75, and 7 hrs after dose administration

Caffeine Breath Test The caffeine test was only conducted in slow metabolizers on day 7. The ^{13}C-labelled caffeine dose (3 mg/kg) was dissolved in 200 ml water then administered to the subjects. The amount of ^{13}C-labelled CO_2 was measured in breath at selected intervals over 8 hrs after administration of the caffeine dose.

PD Sampling Gastric secretion was only assessed in rapid metabolizers. Samples were aspirated from the gastric content through a nasogastric tube in 15 min aliquots. After collection of the 2nd sample (30 min), IV pentagastrin (90 µg.hr) was administered and gastric acid aliquots were collected for 4 × 15 min periods.

Analysis Method [redacted] was used to assay H 199/18, H 199/19, omeprazole and their sulphone metabolites in plasma, while method [redacted] was used to assay the hydroxy metabolites.

Results and Conclusions

- No consistent changes were noted in caffeine metabolism with H 199/18, H 199/19 or omeprazole, which implies that those compounds do not appreciably inhibit CYP 1A2 enzyme.

- The three compounds tested in this study seemed to have similar AUC vs. effect relationships. Administration of H 199/18 resulted in the highest degree of acid inhibition, which might be due to a higher AUC compared to the two other compounds.

- Based on $AUC_{0\rightarrow\infty}$, the ratio between slow and rapid metabolizers was greatest for H 199/19 and smallest for H 199/18. It was also noted that AUC increased with multiple dose administration of all three compounds in rapid metabolizers, but not in slow metabolizers.

Reviewer's Comments

- *Large inter-individual variability was noted with the caffeine breath test data, which casts doubt into the reliability of the test for evaluating the in vivo induction activity of omeprazole and its enantiomers on CYP 1A2 enzymes.*

- *Omeprazole has already been shown to induce CYP 1A2 in vivo in a dose-dependent manner (Rost et al, 1994 & Nousbaum et al, 1994). Using caffeine as a marker for CYP 1A2 metabolic activity, Rost et al demonstrated in 1999 that omeprazole induces CYP 1A2 activity in a weak manner. Hence, even if H 199/18 had a potential to induce CYP 1A2 similar to omeprazole, it is unlikely this would be of any clinical relevance.*

- *The three compounds tested showed similar AUC-effect relationships in the current study. However, only one dose was evaluated (i.e- the AUC-effect range explored in the study was limited).*

Table 6. Individual data of the cumulative increase of ^{13}C-labelled CO_2 in the breath compared to the baseline curve in slow metabolisers during administration of 60 mg of omeprazole, H 199/18 or H 199/19.

Subject	% increase on ^{13}C-labelled CO_2		
	omeprazole	H 199/18	H 199/19
1			
3			
4			
5			

Table 7. Individual $AUC_{0-\infty}$ (µmol*h/L) of the parent compounds in slow metabolisers on day 1 and day 7 during administration of 60 mg of omeprazole, H 199/18 and H 199/19.

Subject	Day 1			Day 7		
	omeprazole	H 199/18	H 199/19	omeprazole	H 199/18	H 199/19
1						
3						
4						
5						
6						
Geom. mean	30.1	22.6	37.9	31.2	21.7	38.1
Mean	30.4	22.7	38.1	31.4	21.8	38.3

Table 8. Individual $AUC_{0-\infty}$ (µmol*h/L) of the parent compounds rapid metabolisers on day 1 and day 7 during administration of 15 mg of omeprazole, H 199/18 and H 199/19.

Subject	Day 1			Day 7		
	omeprazole	H 199/18	H 199/19	omeprazole	H 199/18	H 199/19
1						
2						
3						
4						
Geom. mean	0.437	0.645	0.339	0.665	1.36	0.308
Mean	0.520	0.834	0.376	0.789	1.57	0.343

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Attachment 1

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Statistical Review: NDA 21-153, H 199/18 Delayed-Release Capsules, AstraZeneca LP

Documents reviewed: NDA 21-153 Pharmacokinetic Section, volume 1.58.

This review concerns the sponsor's open, randomized two-stage group sequential single dose crossover bioequivalence (BE) study comparing the test product (T) and the reference product (R).

Study Design

The study was a two-sequence, two-period, two-treatment crossover study carried out in two stages. The treatments studied were:

test product (T):	H 199/18 market capsule 20 mg., batch number H 1189-06-01-05.
reference product (R):	H 199/18 phase III capsule 20 mg., batch number H 1189-04-01-05.

The study subjects were treated in two sequential groups. The first group consisted of subjects 1-36 and the second group consisted of subjects 37-72. The date of first treatment administration (period 1) for each subject was as follows:

subject number	period 1 start date
1-12	03/15/99
13-24	03/16/99
25-36	03/17/99
37-49	05/18/99
50-61	05/19/99
62-72	05/20/99

For the majority of the subjects the washout period (difference between the start date for period 2 and the start date for period 1) was 7 days. The washout period was 8 days for subjects 4, 9, 18, and 53, and the washout period was 9 days for subject 12.

PK Responses Analyzed

The sponsor carried out statistical analyses on the standard PK responses AUC_t, AUC (extrapolated to infinity), and Cmax. In all cases, statistical analysis was carried out on log-transformed PK responses. For this review, I have extracted the Cmax data from Appendix 16.2.5 for reanalysis.

Group Sequential Study Design

The main issue in this review is the sponsor's use of a group sequential study design for their BE study. As described in their protocol, the study design called for an initial group of 36 subjects in a standard two-treatment crossover design. If 94% confidence intervals for the ratio of the geometric mean for T over the geometric mean for R fell within the standard equivalence limits of 80% to 125% for all three PK parameters (AUC_t, AUC, and Cmax), the study would be terminated and a conclusion of bioequivalence would be reached. If the 94% confidence intervals did not fall within the limits of 80% to 125% for any of the three PK parameters, an additional 36 subjects would be studied. After completion of this second group of 36 subjects, 94% confidence intervals would again be calculated using the data from both groups (72 subjects). If these 94% confidence intervals all fell within the limits of 80% to 125%, a conclusion of bioequivalence would be reached.

In analyzing a BE study for regulatory purposes, one of the objectives of the analysis is to maintain the chosen level of significance, also known as the Type-I error rate. For BE studies, the level of significance is typically set at 0.05 (i.e. 5 percent.) For any given PK parameter, maintaining the chosen level of significance at 5% means that if the true ratio of geometric means for T and R really is less than 80%, or greater than 125%, there is no more than a 5% chance that the product will pass the test for that PK parameter. For standard one stage BE studies, this is accomplished by using a 90% confidence interval to carry out the test. However, it is well known that if a study is carried out in a group sequential fashion, such as was done in this case, use of 90% confidence intervals at each stage will not insure an overall level of significance of 5%. In order to maintain the level of significance at 5%, the sponsor has replaced the standard 90% confidence intervals with more stringent 94% confidence intervals at each stage. This is equivalent to doing the two one-sided tests procedure at each stage at the 3%, rather than the 5%, level of significance.

In choosing 94% as the confidence level to be used at each stage of the study, the sponsor cites a standard reference on group sequential designs:

> Pocock SJ. Interim Analyses for Randomized Clinical Trials: The Group Sequential Approach. *Biometrics 1982,38,153-162.*

However, the sponsor adds a note regarding the Pocock reference:

> This paper describes a slightly different situation. Pocock's method must be adapted to bioequivalence trials and t-distribution.

The method by which the sponsor decided on 94% as the confidence level for each stage is not described in the documents reviewed. However, I have carried out a simulation study of the approach, assuming a within-subject standard deviation on the log scale of 0.31 (this is the estimated within-subject standard deviation obtained from analyses of the sponsor's Cmax data).

My simulation indicates that use of 94% confidence intervals at each stage does indeed maintain the overall level of significance at approximately 5% for the case of a two stage study with 36 subjects per stage.

My Analyses of Cmax

The sponsor indicates that after the first stage (36 subjects) of the study, the 94% confidence intervals for AUC_t and AUC fell within the limits of 80% to 125%, but the 94% confidence interval for Cmax did not. The sponsor thus carried out the second stage (36 additional subjects, for a total of 72). Using data from both stages, the 94% confidence intervals fell within 80% to 125% for all three PK parameters.

In order to check the sponsor's calculations I extracted the Cmax data from Appendix 16.2.5 of the sponsor's Clinical Study Report. Here are the results of my Cmax analyses (like the sponsor, all of my Cmax analyses used log-transformed Cmax's):

1. Although not all subjects within a group started the study on the same calendar date (see above), there is no statistical evidence of any effect due to different start dates within a period. For this reason, I am assuming the usual statistical model – with factors for sequences, subjects, periods, and treatments – for each group.

2. There is no evidence of a group-by-treatment statistical interaction. That is, there is no evidence that the difference between the treatments, T and R, depends on which group is considered. For this reason, I did not include group-by-treatment interaction as a factor in my statistical model for the analysis of both groups.

3. The 94% confidence intervals I obtained for the ratio of geometric means of T and R are:

data analyzed	point estimate	94% confidence interval
first 36 subjects (group 1) only	111.81%	97.24% , 128.57%
all 72 subjects (both groups)	111.74%	101.26% , 123.32%

These results for the analysis of both groups agree with those reported by the sponsor.

The SAS statements I used to obtain these confidence intervals were:

for group 1 only

```
PROC GLM DATA=FIRST;
CLASS SEQ SUBJ PER TRT;
MODEL LCMAX = SEQ SUBJ(SEQ) PER TRT;
LSMEANS TRT/PDIFF CL ALPHA=0.06;
```

for both groups

```
PROC GLM DATA=ALL;
CLASS GRP SEQ SUBJ PER TRT;
MODEL LCMAX = GRP SEQ GRP*SEQ SUBJ(GRP*SEQ) PER GRP*PER TRT;
LSMEANS TRT/PDIFF CL ALPHA=0.06;
```

where LCMAX is the natural logarithm of Cmax.

4. It is interesting to note that by studying such an unusually large number (72) of subjects, the sponsor was able to establish bioequivalence with respect to Cmax for this highly-variable drug (the within-subject CV for Cmax is estimated to be around 32%), even though the point estimate for the ratio of geometric means is almost 112%. This is consistent with the standard application of the Average Bioequivalence criterion.

5. An unusual feature of the Cmax dataset is that group 2 (subjects 37-72), taken by themselves, exhibit a statistically significant (p=0.0260) sequence effect. However, in the analysis of both groups the sequence effect is not statistically significant (p=0.1179). In accordance with standard practice (see the July 1992 Guidance: Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design), such a sequence effect would be ignored in the BE analysis of a drug for which the drug substance does not naturally occur in the body and for which there was no drug detected in the time-zero blood samples in period 2 of the study, as was the case here.

Summary

1. The sponsor has used a group sequential study design for their bioequivalence study. Their method is based on a standard approach (see the sponsor's Pocock reference). Based on simulation, the sponsor's use of 94% as the confidence level to be used for analyses at each stage of the study appears to maintain the overall significance level at around 5%, as we require.

2. Applying this approach, the sponsor was able to establish average bioequivalence for AUC_t, AUC (extrapolated to infinity), and Cmax. I have verified the sponsor's calculations for Cmax, the most variable of the three PK parameters.

/S/

Donald J. Schuirmann
Expert Mathematical Statistician
Quantitative Methods & Research staff

/S/ 8/4/00

Concur: Stella Green Machado, Ph.D.
Director, Quantitative Methods & Research staff

cc:
Original NDA 21-153
HFD-870 Suliman Al Fayoumi
HFD-870 Suresh Doddapaneni
HFD-705 QMR Chron
HFD-705 Stella G. Machado
HFD-705 Donald J. Schuirmann

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Attachment 2

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Draft

Labeling

CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA: 21-154

Submission Date: 2/28/00

Drug: Esomeprazole magnesium (Nexium®)
20 and 40 mg Delayed-Release Capsules

Applicant's Proposed Indication:

Triple Therapy (NEXIUM™ plus amoxicillin and clarithromycin): NEXIUM™, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and active or a history of duodenal ulcer disease to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

Applicant: AstraZeneca LP
Wayne, PA

Type of Submission: New NDA

Category: 1, 4S

OCPB Reviewer: Joette M. Meyer, Pharm.D.

I. BACKGROUND

Esomeprazole (formerly H199/18) is the S-enantiomer of the proton pump inhibitor omeprazole. The applicant is seeking approval for a 10-day triple therapy treatment regimen in combination with clarithromycin and amoxicillin in patients with duodenal ulcer disease or a history of duodenal ulcer disease for the eradication of *Helicobacter pylori* to reduce the risk of duodenal ulcer recurrence.

Omeprazole was approved in the US in 1988 for the treatment of acid-related disorders. Subsequently, it was also approved for the treatment of *H. pylori* infection in patients with duodenal ulcer disease or a history of duodenal ulcer disease to reduce the risk of duodenal ulcer recurrence as a dual therapy (1996) with clarithromycin for 14 days and as a triple therapy (1998) with clarithromycin and amoxicillin for 10 days.

Esomeprazole (NDA 21-153) was submitted on 12/3/99 to the Division of Gastrointestinal and Coagulation Drug Products for the following three indications:

- acute healing of erosive esophagitis (EE)
- symptomatic gastroesophageal reflux disease
- maintenance of healing of EE

Clinical Pharmacology/Biopharmaceutics

Item 6 of this submission (Human Pharmacokinetics and Bioavailability) is comprised of 40 volumes containing data from 39 Phase I studies. The basic pharmacokinetic parameters, including bioavailability, for esomeprazole are characterized in single and multiple dose pharmacokinetic studies in healthy subjects and special patient populations (hepatic impairment). The bioequivalence of the esomeprazole formulation used in Phase III and the to-be-marketed formulation is documented under fasting conditions. Food effects, the effects of age and gender, and various drug-drug interactions were studied (including two studies evaluating the interaction between esomeprazole, amoxicillin, and clarithromycin). The validation and performance of the analytical methods is documented.

Reviewer's Comment: The Biopharm review for all the included studies was completed by Suliman I. Al-Fayoumi, Ph.D., Clinical Pharmacology /Biopahrmaceutics Reviewer in HFD-180 (DGCDP) and filed with NDA 21-153.

II. LABELING COMMENTS (previously discussed with the applicant)

1. *To specify the specify dosing of esomeprazole in relation to meals, please add the following sentence to the label. This recommendation is based on pharmacokinetic data reviewed by Dr. Al-Fayoumi.*

   (a) ***CLINICAL PHARMACOLOGY, Pharmacokinetics,*** *Absorption*

   Esomeprazole should be taken —— one —— hour before meals.

   (b) ***PRECAUTIONS, Information for Patients***

   NEXIUM Delayed-Release Capsules should be taken —— one —— hour before meals.

   (c) ***DOSAGE AND ADMINISTRATION***

   NEXIUM Delayed-Release Capsules should be swallowed whole and taken —— one —— hour before meals.

2. *Please add the following wording to the **CLINICAL PHARMACOLOGY** section of the label to address the drug-interaction between esomeprazole and clarithromycin. The supporting data can be found in Study SH-QBE-0034.*

   Pharmacokinetics: Combination Therapy with Antimicrobials
   Esomeprazole magnesium 40 mg once daily was given in combination with clarithromycin 500 mg twice daily and amoxicillin —— twice daily for 7 days to 17 healthy male and female subjects. The mean steady state AUC and C_{max} of esomeprazole increased by 70% and 18%, respectively, during triple combination therapy compared to treatment with esomeprazole alone. The observed increase in esomeprazole exposure during co-administration with clarithromycin and amoxicillin is not expected to produce significant safety concerns.

The pharmacokinetic parameters for clarithromycin and amoxicillin were similar during triple combination therapy and administration of each drug alone. However, the mean AUC and C_{max} for 14-hydroxyclarithromycin increased by 19% and 22%, respectively, during triple combination therapy compared to treatment with clarithromycin alone. This increase in exposure to 14-hydroxyclarithromycin is not considered to be clinically significant.

3. *To address the pharmacokinetics of esomeprazole in patients with hepatic impairment, please add the following paragraphs to the label. The supporting data can be found in Studies SH-QBE-0008 and SH-QBE-0026.*

(a) ***CLINCIAL PHARMACOLOGY, Special Populations,*** *Hepatic Insufficiency*

(b) ***DOSAGE AND ADMINISTRATION, Special Populations,*** *Hepatic Insufficiency*

No dosage adjustment is necessary in patients with mild to moderate liver impairment (Child Pugh Classes A and B). patients with severe hepatic insufficiency (Child Pugh Class C), a dose of 20 mg once daily should not be exceeded. (See **CLINICAL PHARMACOLOGY-Pharmacokinetics**.)

4. *Please add the following paragraphs to the* ***PRECAUTIONS, Drug Interactions*** *section of the label to address the drug-interaction between esomeprazole and clarithromycin and clarithromycin and pimozide.*

Combination Therapy with Clarithromycin

Co-administration of esomeprazole, clarithromycin, and amoxicillin have resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin. (See **CLINICAL PHARMACOLOGY**, Pharmacokinetics: Combination Therapy with Antimicrobials.)

Concomitant administration of clarithromycin with pimozide is contraindicated (see clarithromycin package insert).

III. RECOMMENDATION

The information contained in Item 6 of NDA 21-154 is adequate to support approval.

/S/ 12/12/00

Joette M. Meyer, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Funmi Ajayi, Ph.D. (Team Leader) /S/ 12/12/00

cc: HFD-590: /NDA 21-154
/PM/Fritsch
HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ

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