DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0036		
VERSION NO.	01		
STUDY CODE	SH-QBE-0036		
DATE	28 May, 1999		

An interaction study between H 199/18 and cisapride in healthy male and female subjects

STUDY CENTRE(S)

Single centre study

STUDY PERIOD

			PHASE OF DEVELOPMENT
-	**DATE OF FIRST ENROLMENT**	11 February, 1998	I
-	**DATE OF LAST COMPLETED**	1 April, 1998	

OBJECTIVES

The primary objective of this study was to investigate any potential pharmacokinetic interactions between H 199/18 and cisapride during repeated oral administration to healthy subjects. The secondary objective was to assess the safety of H 199/18 and the combination of the two drugs.

STUDY DESIGN

Open, randomised, three-way cross-over study

MAIN CRITERIA FOR INCLUSION

Healthy male and female subjects

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 capsule 40 mg, batch no. H 1222-04-01-05, oral dose of 40 mg o.m.
Cisapride (Prepulsid®) tablet 10 mg, batch no. H 1073-02-01-03, oral dose of 20 mg b.i.d.

DURATION OF TREATMENT

Three treatment periods, each consisting of seven days. The periods were separated by wash-out periods of at least two weeks.

MAIN VARIABLES:

- PHARMACOKINETICS

The main pharmacokinetic variables were the area under the plasma concentration-time curve during the dosing interval (AUC_τ; $\tau = 24$ h for H 199/18 and 12 h for cisapride), the observed maximum plasma concentration (C_{max}) and the plasma elimination half-life ($t_{1/2}$).

- SAFETY

The ECG-parameters QTc and interlead dispersion assessed 1.5 and 3 hours post-dose

STATISTICAL METHODS

The log-transformed variables AUC_τ, C_{max} and $t_{1/2}$ were analysed using a mixed model ANOVA (Analysis of variance) with fixed effects for sequence, period and treatment and a random effect for subject within sequence. Data for H 199/18 and for cisapride were analysed separately. The results were in the end anti-logarithmized and stated as:

a) Estimates and 95% confidence intervals for the true geometric means of AUC_τ, C_{max} and $t_{1/2}$.
b) Estimates and 95% confidence intervals for the true ratios [(cisapride+H 199/18)/cisapride or 199/18 alone] of AUC_τ, C_{max} and $t_{1/2}$ and p-values for the corresponding tests of equal geometric means.

The ECG variables QTc and interlead dispersion were analysed and presented using log-transformed values for the QT_c, but with non-transformed values for dispersion. Separate analyses were made for the ECG assessments made at 1.5 and 3 hours post-dose on day 7 of each treatment period.

SUBJECTS

	Total
No. planned	18
No. randomised and treated	24
Males/Females	13/11
Mean age (range)	25.2 years (21-31)
No. analysed for pharmacokinetics	23 (H 199/18 and combination), 22 (cisapride and combination)
No. analysed for safety	24
No. completed	22

SUMMARY

- PHARMACOKINETIC RESULTS

As shown in Tables 1-3, for cisapride, AUC_τ was 32% larger and $t_{1/2}$ was 31% longer following coadministration with H 199/18 compared to the period with cisapride alone. There was a 10% increase in C_{max} which was not statistically significant. The median t_{max} was 1.4 hours and 1.0 hour, respectively, after each treatment.

For H 199/18, no changes in AUC_τ, C_{max} or $t_{1/2}$ were observed after coadministration with cisapride compared to the period with H 199/18 alone (Tables 1-3). The median t_{max} was 1.0 hour and 1.5 hours, respectively, after each treatment.

Table 1. **Geometric means and the ratios of geometric means of AUC_τ ($\mu mol \cdot h/L$) for H 199/18 and cisapride following seven days oral treatment with H 199/18 capsule 40 mg o.m. alone and in combination with cisapride tablet 20 mg b.i.d.. Estimates, limits for 95% CI and a p-value for the test of equal geometric means are presented (n=23).**

	Geometric mean	95% confidence interval lower	upper	p-value
H 199/18				
H 199/18 with cisapride (B)	13.92	11.85	16.35	
H 199/18 alone (A)	13.90	11.84	16.33	
B/A	1.00	0.87	1.15	0.99
Cisapride				
H 199/18 with cisapride (B)	1.48	1.27	1.73	
cisapride alone (C)*	1.12	0.96	1.31	
B/C*	1.32	1.20	1.46	<0.001

* n = 22

Table 2. **Geometric means and the ratios of geometric means of C_{max} ($\mu mol/L$) for H 199/18 and cisapride following seven days oral treatment with H 199/18 capsule 40 mg o.m. alone and in combination with cisapride tablet 20 mg b.i.d.. Estimates, limits for 95% CI and a p-value for the test of equal geometric means are presented (n=23).**

	Geometric mean	95% confidence interval lower	upper	p-value
H 199/18				
H 199/18 with cisapride (B)	5.41	4.72	6.21	
H 199/18 alone (A)	5.15	4.49	5.91	
B/A	1.05	0.91	1.22	0.49
Cisapride				
H 199/18 with cisapride (B)	0.18	0.16	0.20	
cisapride alone (C)*	0.16	0.14	0.19	
B/C*	1.10	0.97	1.24	0.15

* n = 22

Table 3. **Geometric means and the ratios of geometric means of $t_{1/2}$ (h) for H 199/18 and cisapride following seven days oral treatment with H 199/18 capsule 40 mg o.m. alone and in combination with cisapride tablet 20 mg b.i.d.. Estimates, limits for 95% CI and a p-value for the test of equal geometric means are presented (n=23).**

	Geometric mean	95% confidence interval lower	upper	p-value
H 199/18				
H 199/18 with cisapride (B)	1.46	1.32	1.61	
H 199/18 alone (A)	1.42	1.29	1.57	
B/A	1.02	0.96	1.10	0.46
Cisapride				
H 199/18 with cisapride (B)	9.72	8.76	10.78	
cisapride alone (C)*	7.42	6.69	8.23	
B/C*	1.31	1.17	1.47	<0.001

* n=22

- **SAFETY RESULTS**

As shown in Table 4, the estimates of geometric means for QTc-interval at 1.5 and 3 hours post-dose after treatment with cisapride in combination with H 199/18 were similar to those after treatment with cisapride alone, but significantly higher than QTc-intervals assessed after treatment with H 199/18 alone.

The changes in individual QTc values during treatment with H 199/18 alone were $\leq$ 30 ms. The changes in individual QTc values during tratment with cisapride alone and in combination with H 199/18 were similar and $\leq$ 60 ms.

No statistically significant differences in dispersion between treatments were observed, and all dispersion values were within normal limits.

Table 4. **Geometric means and the ratios of geometric means of QTc $(msec)$ at 1.5 and 3 hours post-dose, following seven days oral treatment with H 199/18 capsule 40 mg o.m. alone and in combination with cisapride tablet 20 mg b.i.d.. Estimates, limits for 95% CI and a p-value for the test of equal geometric means are presented (n=23).**

	Geometric mean	95% confidence interval lower	upper	p-value
1.5 hours post-dose				
H 199/18 alone (A)	400.77	392.40	409.32	
H 199/18 with cisapride (B)	412.52	403.91	421.32	
cisapride alone (C)*	412.69	404.10	421.46	
B/A	1.03	1.01	1.05	0.009
B/C*	1.00	0.98	1.02	0.97
3 hours post-dose				
H 199/18 alone (A)	400.07	391.64	408.69	
H 199/18 with cisapride (B)	418.56	409.73	427.57	
cisapride alone (C)*	416.43	407.67	425.38	
B/A	1.05	1.02	1.07	<0.001
B/C *	1.01	0.98	1.03	0.69

* n = 22

DATE OF THE REPORT

28 May, 1999