ASTRA
ASTRA HÄSSLE

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0026		
VERSION NO.	01		
STUDY CODE	SH-QBE-0026		
DATE	2 May, 1999		

Pharmacokinetics of H 199/18 and its main metabolites in patients with varying degrees of impaired liver function.

STUDY CENTRE

Single centre study

STUDY PERIOD

- **DATE OF FIRST ENROLMENT** 25 February, 1998
- **DATE OF LAST COMPLETED** 10 September, 1998

PHASE OF DEVELOPMENT

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OBJECTIVES

The primary objective was to study the pharmacokinetics of H 199/18 and its main metabolites after repeated dosing in patients with varying degrees of impaired liver function. The secondary objective was to evaluate the safety of H 199/18.

STUDY DESIGN

Open one-way study

MAIN CRITERIA FOR INCLUSION

Male and female patients with varying degrees of liver dysfunction classified according to the definition by Child-Pugh.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 capsule 40 mg, batch no. H 1222-04-01-04, oral dose of 40 mg o.m.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

None

DURATION OF TREATMENT

Five days

MAIN VARIABLES

The area under the plasma concentration versus time curve during a dosage interval (AUC_τ), the observed maximum plasma concentration (C_{max}), the plasma elimination half-life ($t_{1/2}$) and the time of maximum plasma concentration (t_{max}).

STATISTICAL METHODS

Descriptive statistics (mean, SD, median, min, max, geometric mean) were calculated for the pharmacokinetic parameters. Also 95 % confidence intervals were calculated for the true geometric mean, using quantiles from the Student´s t-distribution.

The pharmacokinetic parameters in the present study were compared with those obtained in a previous study. In that study, patients with symptomatic GERD without liver dysfunction received 40 mg H 199/18 once daily for 5 days. For the comparison the log-transformed AUC_τ, C_{max} and $t_{1/2}$ were each analysed in a linear model with sex and age as covariates. The results are presented as estimates of the ratios for patients with liver dysfunction to GERD patients without liver dysfunction with 95% confidence intervals for the estimated ratios.

PATIENTS

	Total
No. planned	12
No. randomised and treated	13
Males/Females	9/4
Mean age (range)	50.5 years (40-60)
No. analysed for clinical pharmacology	12
No. analysed for safety	13
No. completed	12

SUMMARY

- **CLINICAL PHARMACOLOGY RESULTS**

Four patients were classified as having mild impairment of liver function (Child A), four as having moderate impairment of liver function (Child B) and four as having severe impairment of liver function (Child C). The estimated geometric mean pharmacokinetic parameters of H 199/18, the hydroxy metabolite and the sulphone metabolite are summarised in Table 1.

Table 1. Geometric means of AUC_τ (µmol·h/L), C_{max} (µmol/L) and $t_{1/2}$ (h) of H 199/18 and its metabolites on day 5 following daily oral doses of 40 mg H 199/18 as a capsule to patients with liver dysfunction (n=12). Estimates and limits for 95% CI are presented.

Substance	Pharmacokinetic variable	Estimated geometric mean	95 % confidence interval lower	upper
H 199/18	AUC_τ	23.06	18.75	28.37
	C_{max}	6.09	4.95	7.50
	$t_{1/2}$	2.11	1.55	2.89
Hydroxy	AUC_τ	1.93	1.36	2.75
	C_{max}	0.23	0.17	0.31
	$t_{1/2}$	5.37	3.16	9.14
Sulphone	AUC_τ	37.89	30.74	46.71
	C_{max}	2.72	2.36	3.14
	$t_{1/2}$	7.31	5.14	10.38

H 199/18 was rapidly absorbed with a mean t_{max} of approximately 2 hours. The plasma levels of H 199/18 were higher in patients with liver dysfunction than in GERD patients without liver dysfunction. The estimated value of AUC_τ of H 199/18 was 76% (95% CI; 29 to 142%) higher. The estimated value of C_{max} was 26% (95% CI; -6 to 69%) higher and that of $t_{1/2}$ was 29% (95% CI; -1 to 68%) higher compared to GERD patients. However, when the patients were grouped according to the degree of liver dysfunction the AUC_τ and $t_{1/2}$ values in patients with mild and moderate liver dysfunction were in the same range as those for GERD patients.

- **SAFETY RESULTS**

Three adverse events were reported for three of the 13 patients during active treatment with H 199/18, and four AEs were present during the follow-up period. Adverse events were few and mild or moderate in intensity. Most AEs could be related to the underlying liver insufficiency. One patient was hospitalised due to hepatic encephalopathy. This was regarded as a serious adverse event but was judged mainly to be due to withdrawal of lactulose and not related to H 199/18.

DATE OF THE REPORT

11 May, 1999