ASTRA
ASTRA HÄSSLE

DRUG PRODUCT	H 199/18	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0038		
VERSION NO.	01		
STUDY CODE	SH-QBE-0038		
DATE	7 May, 1999		

An interaction study between H 199/18 and warfarin in warfarin-treated patients.

STUDY CENTRE

Single centre study

STUDY PERIOD

- **DATE OF FIRST ENROLMENT** 27 January, 1998
- **DATE OF LAST COMPLETED** 17 June, 1998

PHASE OF DEVELOPMENT

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OBJECTIVES

The primary objectives were to determine the effect of H 199/18 on the steady-state plasma concentrations and anticoagulant effect of warfarin in warfarin-treated patients. The secondary objective was to evaluate the tolerability of H 199/18 in warfarin-treated patients.

STUDY DESIGN

Double-blind, randomised, two-way cross-over study

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Patients stabilised on warfarin

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.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Placebo capsule, batch no. H 0459-06-03-06, oral dose o.m.

DURATION OF TREATMENT

Two periods of three weeks

MAIN VARIABLES:

The anticoagulant effect and the trough plasma concentrations of R- and S-warfarin were the primary variables.

STATISTICAL METHODS

The log-transformed values for the geometric means of the PK values, the blood coagulation times and the trough plasma concentrations of R- and S-warfarin assessed on the last two days of treatment period 1 (visits 7-8) and treatment period 2 (visits 11-12) were analysed using a mixed model ANOVA (Analysis of variance), with fixed effects for sequence, period and treatment (H 199/18 or placebo) and a random effect for patient within sequence.

The results were finally anti-logarithmized and are stated as:
a) Estimates and 95% confidence intervals for the true geometric means for PK values, coagulation times and the trough plasma concentrations
b) Estimates and 95% confidence intervals for the true ratios (warfarin with H 199/18/warfarin with placebo) of PK values, coagulation times and the trough plasma concentrations, together with p-values for tests of equal geometric means.

According to international guidelines, lack of metabolic drug-drug interaction could in general be concluded if the 90% confidence interval for the ratio of the relevant pharmacokinetic parameters with and without the interacting drug fells within the range 0.80-1.25. However, due to the narrow therapeutic index of warfarin, the 95% confidence interval was considered more appropriate in the evaluation of this study.

The results of separate analyses are presented for the 26 patients analysed according to the Intention To Treat (ITT) approach and for the 22 patients analysed according to the Per Protocol (PP) approach.

PATIENTS

	Total
No. planned	30
No. randomised/treated	30/29
Males/Females	21/9
Mean age (range)	54.5 (27-68) years
No. analysed for clinical pharmacology	ITT26/PP22
No. analysed for safety	29
No. completed	27

SUMMARY

- **CLINICAL PHARMACOLOGY RESULTS**

The mean trough plasma concentration of R-warfarin was increased by 13% during H 199/18 treatment compared to placebo, whilst that of S-warfarin was unchanged (Table 1). The PK values and the coagulation times were stable throughout the entire study period (Table 2).

The results for a PP analysis were consistent with those observed for the ITT analysis reported below.

Table 1. Geometric means and their ratio for trough plasma concentrations (μmol/L) of R- and S-warfarin during repeated administration of 40 mg H 199/18 or placebo. Estimates, limits for 95% CI and a p-value for the test of equal geometric means are presented (ITT, n=26).

	Geometric mean	95% confidence interval lower	upper	p-value
R-Warfarin				
H 199/18 (A)	2.78	2.32	3.32	
Placebo (B)	2.46	2.06	2.94	
A/B	1.13	1.07	1.19	<0.001
S-Warfarin				
H 199/18 (A)	1.58	1.35	1.85	
Placebo (B)	1.58	1.35	1.85	
A/B	1.00	0.95	1.06	0.93

Table 2. Geometric means and their ratio for the anticoagulant effect of warfarin during repeated administration of 40 mg H 199/18 or placebo. Estimates, limits for 95% CI and a p-value for the test of equal geometric means are presented (ITT, n=26).

	Geometric mean	95% confidence interval lower	upper	p-value
PK-value (%)				
H 199/18 (A)	18.33	16.75	20.07	
Placebo (B)	19.55	17.86	21.40	
A/B	0.94	0.83	1.06	0.28
Coagulation time (s)				
H 199/18 (A)	57.46	53.55	61.65	
Placebo (B)	54.73	51.01	58.73	
A/B	1.05	0.95	1.15	0.30

- **SAFETY RESULTS**

Twenty-four AEs were reported for 16 of the 29 patients during treatment with H 199/18 and 15 AEs were reported for 8 patients during the placebo period. Abdominal pain was the most common AE and all AEs reported were of mild to moderate intensity. SAEs were reported for two patients, one during treatment with H 199/18 and one in the follow-up period after H 199/18 treatment. One of these patients had a medical history of recurrent episodes of vomiting and was now again hospitalised due to vomiting. For the other patient, the underlying disease with multiple cerebral infarctions could well explain the epileptic seizures which led to hospitalisation.

DATE OF THE REPORT

7 May, 1999