ASTRA
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DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0032		
VERSION NO.	01		
STUDY CODE	SH-QBE-0032		
DATE	12 March, 1999		

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

STUDY CENTRE

Single centre study

STUDY PERIOD

- **DATE OF FIRST ENROLMENT** 3 November, 1997
- **DATE OF LAST COMPLETED** 8 January, 1998

PHASE OF DEVELOPMENT

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OBJECTIVES

The primary objective was to study the pharmacokinetics of phenytoin after a single oral dose during repeated oral administration of H 199/18 capsules or placebo in healthy male and female subjects. The secondary objective was to evaluate the safety of H 199/18.

STUDY DESIGN

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

DIAGNOSIS AND 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. H1222-04-01-04, oral dose of 40 mg o.m. for seven days. Phenytoin capsule, 100 mg, batch no. H 1136-01-01-03, oral dose of 300 mg on study day 5.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Placebo, batch no. H 0459-06-03-06, oral dose o.m. for seven days.

DURATION OF TREATMENT

Two periods of seven days separated by at least 14 days.

MAIN VARIABLES:

- **PHARMACOKINETICS**

The main pharmacokinetic variables were the total area under the plasma concentration versus time curve (AUC) and the observed maximum plasma concentration (C_{max}).

STATISTICAL METHODS

The log-transformed values AUC, C_{max} and $t_{½}$ for phenytoin were analysed using a mixed model ANOVA (Analysis of Variance) with fixed effects for sequence, period and treatment and a random effect for subjects within sequence.

The results were then anti-logarithmized and stated as:

a) Estimates (geometric means) of AUC, C_{max} and $t_{½}$ during H 199/18 and placebo treatments, and 95% confidence intervals for the true geometric means.
b) Estimates of the ratios of AUC, C_{max} and $t_{½}$ during H 199/18 treatment to AUC, C_{max} and $t_{½}$ during placebo treatment, respectively, 95% confidence intervals for the true ratios and p-values for a test of equal geometric means during H 199/18 and placebo treatments.

Descriptive statistics for the pharmacokinetic variables of phenytoin and H 199/18 are presented.

SUBJECTS

	Total
No. planned	20
No. randomised and treated	20
Males/Females	18/2
Mean age (range)	26.0 years (20-46)
No. analysed for pharmacokinetics	19
No. analysed for safety	20
No. completed	19

SUMMARY

- PHARMACOKINETIC RESULTS

The AUC of phenytoin increased by 13% during treatment with H 199/18 compared to placebo. The C_{max} of phenytoin increased by 10% and the $t_{1/2}$ was prolonged by 12% during treatment with H 199/18 compared with placebo (Table 1). The t_{max} of phenytoin was 5.0 hours after both treatments.

Table 1. Geometric means of AUC (µmol·h/L), C_{max} (µmol/L) and $t_{1/2}$ (h) for phenytoin and the ratio of the geometric means following a single oral administration of 300 mg phenytoin under repeated oral administration of 40 mg H 199/18 capsules or placebo to healthy subjects (n=19). Estimates, limits for 95% CI and p-values for test of equal geometric means are presented.

	Estimate	95% confidence interval		p-value
		lower	upper	
AUC				
H 199/18 (A)	595.5	510.8	694.3	
Placebo (B)	528.9	453.7	616.7	
A/B	1.13	1.05	1.21	0.002
C_{max}				
H 199/18 (A)	17.8	16.2	19.4	
Placebo (B)	16.2	14.8	17.7	
A/B	1.10	1.00	1.20	0.042
$t_{½}$				
H 199/18 (A)	15.26	13.05	17.85	
Placebo (B)	13.68	11.70	16.00	
A/B	1.12	1.05	1.18	<0.001

- SAFETY RESULTS

A total of 55 AEs was reported for 19 of the 20 subjects during the entire study. Headache, fatigue and flatulence were the most common AEs and were reported in similar frequencies in the H 199/18 and placebo periods. However, headache and fatigue were mainly reported after the administration of phenytoin. All AEs reported were of mild to moderate intensity.

DATE OF THE REPORT

12 March, 1999