Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Asasantin (AGGRENOX®)				
Name of active ingredient: Dipyridamole / ASA 200 mg/25 mg		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 16 May 2002	**Number:** 9.144	**Study period (years):** 04/2001 – 05/2001		

Title of study:	A double-blind, randomised, 3-way cross-over study to compare the pharmacokinetics of dipyridamole in three different Asasantin ER extended release (ER) 200 mg dipyridamole/25 mg ASA formulations in healthy male and female volunteers.
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma KG, Germany
Publication (reference):	Not applicable
Clinical phase:	I
Objectives:	Comparative pharmacokinetics of dipyridamole in two new formulations of Asasantin ER compared to the present commercial formulation
Methodology:	Randomised, double-blind, 3-way cross-over trial
No. of subjects entered:	
total:	18
each treatment:	18 Asasantin ER new formulation I (treatment A) 18 Asasantin ER new formulation II (treatment B) 18 Asasantin ER present formulation (treatment C)
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age 21 – 50 years, Broca-Index ± 20 %
Test product:	Asasantin ER capsules (two new formulations with altered production)
dose:	200 mg dipyridamole / 25 mg ASA, b.i.d. on days 1-4, s.i.d. on day 5 of respective treatment period
mode of admin.:	p.o.
batch no.:	102 397 (formulation I) and 102 413 (formulation II)
Duration of treatment:	Five days for each treatment
Reference therapy:	Asasantin ER capsules (present commercial formulation)
dose:	200 mg dipyridamole / 25 mg ASA, b.i.d. on days 1-4, s.i.d. on day 5 of respective treatment period
mode of admin.:	p.o.
batch no.:	101 706

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Asasantin (AGGRENOX®)		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Dipyridamole / ASA 200 mg/25 mg		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 16 May 2002	**Number:** 9.144	**Study period (years):** 04/2001 – 05/2001		

Criteria for evaluation:

Efficacy: Pharmacokinetics: Primary endpoints: AUC_{ss}, %PTF of dipyridamole

Secondary endpoints: $C_{max,ss}$ / AUC_{ss}, $C_{max,ss}$, $C_{min,ss}$, $T_{max,ss}$, AUC_{fluct}, $t_{½}$, Ae% of dipyridamole (dp) and its glucuronide (dp-gluc), Ae% of SA

Safety: Blood pressure, pulse rate, ECG, adverse events, laboratory tests

Statistical methods: Descriptive statistics, 90 % confidence intervals

SUMMARY - CONCLUSIONS:

Efficacy results (Pharmacokinetics):

Point estimators and confidence intervals for primary and secondary parameters derived from plasma concentrations in TABLEs 2: 1 – 2: 2. FIGURE 2: 1 displays geometric means of the three treatments.

TABLE 2: 1 Test/reference ratios, 90 % confidence intervals and intra-individual CV (%) of primary and secondary PK parameters with 50 %-type being test and the commercial formulation as reference (three-way cross-over; source TABLE 14.1: 4)

parameter	lower limit	point estimator	upper limit	intra-ind. CV%
AUC_{ss}	0.91	1.00	1.10	15.3
PTF	0.74	0.91	1.11	33.2
$C_{max,ss}$	0.81	0.94	1.08	23.2
$C_{min,ss}$	0.87	1.09	1.36	37.3
$C_{max,ss}/AUC_{ss}$	0.82	0.94	1.07	21.0
$AUC_{fluc,ss}$	0.75	0.89	1.06	28.0

... dipyridamole\asasantin\9_144\non-compartmental\
bb9_144pk.xls[confid_int]
Source data: TABLE 14.1: 4

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Asasantin (AGGRENOX®)		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Dipyridamole / ASA 200 mg/25 mg		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 16 May 2002	**Number:** 9.144	**Study period (years):** 04/2001 – 05/2001		

TABLE 2: 2 Test/reference ratios, 90 % confidence intervals and intra-individual CV (%) of primary and secondary PK parameters with one pellet type being test and the commercial formulation as reference (three-way cross-over; source TABLE 14.1: 5)

parameter	lower limit	point estimator	upper limit	intra-ind. CV%
AUC_{ss}	0.85	0.94	1.03	15.3
PTF	0.72	0.88	1.08	33.2
$C_{max,ss}$	0.77	0.89	1.02	23.2
$C_{min,ss}$	0.90	1.13	1.41	37.3
$C_{max,ss}/AUC_{ss}$	0.83	0.95	1.08	21.0
$AUC_{fluc,ss}$	0.75	0.90	1.06	28.0

... dipyridamole\asasantin\9_144\non-compartmental\
bb9_144pk.xls[confid_int]
Source data: TABLE 14.1: 5

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Asasantin (AGGRENOX®)		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Dipyridamole / ASA 200 mg/25 mg		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 16 May 2002	**Number:** 9.144	**Study period (years):** 04/2001 – 05/2001		

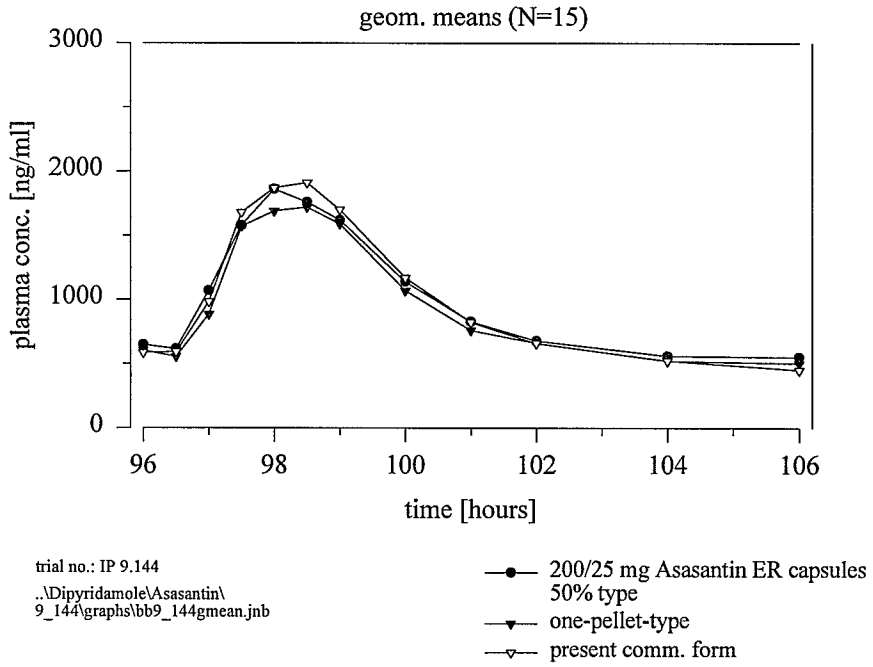

FIGURE 2: 1 Geometric means of analyte dipyridamole at steady-state interval (96 – 106 h) after administration of 50% type, one pellet type and commercial ASASANTIN ER (N = 15) (source TABLEs 16.3.2: 1 - 3)

The results indicate clearly that pharmacokinetics of the 50% type is bioequivalent to the commercial formulation for both primary endpoints, the one pellet type is bioequivalent with regard to $AUC_{SS.}$ Thus the commercial product can be replaced by the 50 %-type, the one pellet type needs a small modification of production in order to be bioequivalent.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Asasantin (AGGRENOX®)		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Dipyridamole / ASA 200 mg/25 mg		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 16 May 2002	**Number:** 9.144	**Study period (years):** 04/2001 – 05/2001		

Safety results:

The predominant adverse event was headache (together with nausea and/or vomiting) which is known to be typical for dipyridamole. However, in most cases subjects developed tolerance to headache during the course of the trial. Three of eighteen subjects (one in each treatment) discontinued due to severe headache.

There were no changes in vital signs, physical findings or other observations as related to safety. There were no abnormal electrocardiograms and changes related with treatment.

Conclusions:

The results indicate clearly that pharmacokinetics of the 50% type is bioequivalent to the commercial formulation for both primary endpoints, the one pellet type is bioequivalent with regard to $AUC_{ss.}$ Thus the commercial product can be replaced by the 50% type, the one pellet type needs a small modification of production in order to be bioequivalent.