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***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Aggrenox®				
Name of active ingredient: Dipyridamol, ASA		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 28 Apr 2003	**Number:** U03-1269	**Study period (years):** Sep 2002 - Oct 2002		

Title of study:	Bioavailability of dipyridamole after Asasantin (extended release 200mg dipyridamole/25mg ASA) in 3 experimental formulations (given b.i.d. over 3 or 5 days, respectively) relative to the standard formulation in 16 healthy female and male subjects. Intraindividual comparison, randomised, open.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre Boehringer Ingelheim Pharma GmbH & Co. KG D-88397 Biberach an der Riss, Germany
Publication (reference):	N/A
Clinical phase:	I
Objectives:	Comparative pharmacokinetics of dipyridamole in three new formulations of Asasantin ER compared to the present commercial formulation
Methodology:	Randomised, open label, 4-way cross-over trial
No. of subjects:	
planned:	entered: 16
actual:	enrolled: 16
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age $\geq$18 and $\leq$60 years, BMI $\geq$18.5 and $\leq$29.9 kg/m^2
Test product:	Asasantin ER capsules (three new formulations with altered production)
dose:	200 mg dipyridamole/25 mg ASA b.i.d
mode of admin.:	p.o.
batch no.:	New formulation l "low": 203240 New formulation 2 "high": 203232 New formulation 3"medium": 203237
Duration of treatment:	3 or 5 days, respectively
Reference therapy:	Asasantin ER capsules (present commercial formulation)
dose:	200 mg dipyridamole/25 mg ASA b.i.d
mode of admin.:	p.o.
batch no.:	203293

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Criteria for evaluation:

Efficacy: Pharmacokinetics:
Primary endpoints: %Ae of dipyridamole over the two last treatment days
Secondary endpoints: $\%Ae_{1\text{-}3h}$, $\%Ae_{8\text{-}10h}$, $(\%Ae_{1\text{-}3h}\text{-}\%Ae_{8\text{-}10h})$ / %Ae0-10h

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

Statistical methods: Descriptive statistics, 90 % confidence intervals

SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetics:
Due to the high frequency of dropouts, no adequate pharmacokinetic analysis was possible. In order to find out whether unusually high absorption might have contributed to the high incidence of side effects, total urinary excretion of each dosing event was investigated. Geometric means of urinary excretion of the first three dosing events were 2.83 % for high, 2.18 % for medium, 2.42 % for low release and 2.47 % for the commercial preparation.

As interindividual variability is at least as large as difference between treatments, no conclusions on performance of test preparations versus reference can be drawn.

Overall urinary excretion was in the normal range. Therefore extent of absorption did not cause the high incidence of side effects.

Safety results:

The symptoms reported coincide well with the known vasodilator effect of dipyridamole. However incidence and severity were not expected. Severe headache frequently associated with nausea/vomiting led to discontinuation of the trial in 12 out of 16 subjects and thus to discontinuation of the whole trial during the first treatment period.

Conclusions:

In summary no explanation for the high susceptibility of the subjects to the vasodilator effect of dipyridamole could be found.