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 ER (Aggrenox)				
Name of active ingredient: Dipyridamole/ASA 200 mg/25 mg		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 12 March, 2001	**Number:** 9.131	**Study period (years):** 2000		

Title of study:	Tolerability of a two-week treatment with Asasantin extended release 200/25 mg capsules b.i.d, compared to reduced dose during the first week of treatment in a double-blind, randomised, placebo controlled parallel group comparison trial in healthy female and male subjects.
Investigator:	[redacted]
Study center(s):	[redacted]
Publication (reference):	n.a.
Clinical phase:	I
Objectives:	To investigate the occurrence of dipyridamole associated headaches in healthy subjects using a titration scheme or not
Methodology:	multiple dose, randomised, double-blind, placebo controlled trial with parallel group comparison
No. of subjects entered:	
total:	100 (50 female / 50 male)
each treatment:	40-40-20
Diagnosis and main criteria for inclusion:	healthy female and male subjects of 18-55 years old, with a Broca Index of $\geq$ - 20 % and $\leq$ + 20 %
Test product:	Asasantin ER
dose:	200 / 25 mg once a day on days 1-7, b.i.d. on days 8-14
mode of admin.:	Per oral
batch no.:	910215
Duration of treatment:	14 days
Reference therapy 1:	Asasantin ER
dose:	200 / 25 mg, b.i.d. on days 1-14
mode of admin.:	Per oral
batch no.:	910215

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Reference therapy 2:	Placebo
dose:	b.i.d. on days 1-14
mode of admin.:	Per oral
batch no.:	B991204
Criteria for evaluation:	
Efficacy:	Not applicable.
Safety:	AUC (intensity of headache), blood pressure, pulse rate, ECG, adverse events and laboratory tests
Statistical methods:	Wilcoxon-Mann-Whitney and Kruskal Wallis tests for AUC, descriptive statistical analysis

SUMMARY – CONCLUSIONS:

Efficacy results: Not applicable.

Safety results: As could be expected from earlier studies and clinical experience with Asasantin ER, headache was the dominantly reported adverse event and except for the screening period and a few cases under Asasantin or placebo treatment headache was always considered to be drug related. In both active drug groups about 50 % of the subjects reported headache, while only 30 % of the subjects randomised to placebo suffered from headache of any intensity. From the results of the statistical analyses a difference between low and high dose Asasantin ER was not concluded with regard to the occurrence of headache.

Concerning the primary variable of the study – AUC (headache), calculated as the sum of the intensity * duration area – showed significant differences in the comparisons performed between active drug and placebo for period 1 and the combined periods 1 and 2, while no significant differences between Asasantin low starting dose and Asasantin high starting dose were observed for all of the considered periods.

The active drug groups were similar in all intensities, and about 50 % of the subjects experienced headache of moderate or severe degree, compared to 10 % of the subjects treated with placebo. The Chi^2-test for the three arms was significant, while the comparison of the two Asasantin ER groups did not indicate a difference in the intensity distribution. Also no statistical difference in the comparison of the active drug groups was observed with respect to use of ASA to treat or prevent headache.

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	At the end of the study, no new or worsened findings were reported for any subject in the general physical examination and in the 12-lead ECG examination. The global clinical tolerability of each treatment week was judged as good or satisfactory for all subjects with the exception of 11 cases of unsatisfactory tolerability of the active treatments and 3 cases, which were not assessable due to discontinuation. The analysis of vital sign parameters and safety laboratory measurements did not reveal clinically relevant changes, and did not suggest treatment effects.
Pharmacokinetics:	Plasma was collected at days 4 and 11of all treatments. The observed dipyridamole plasma concentrations were in the usual range and indicated a good compliance of all subjects.
Conclusions:	Based on the results of the analyses performed for headache it is concluded that the intake of a reduced Asasantin dose shortly before going to sleep during the first treatment week does not reduce the frequency and intensity of headache episodes. Thus, a reduced Asasantin dose at treatment start cannot be recommended to increase patient compliance.