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				
Name of active ingredient: Acetylsalicylic acid + modified-release dipyridamole		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page: to**		**Addendum No.:**
Report date: 13 November 2000	**Number:**	**Study period (years):** 17 Jan 2000 to 19 May 2000		

Title of study:	A randomised, two-period, cross-over trial to compare the effects of acetylsalicylic acid (75 mg/day) with the combination of acetylsalicylic acid (25 mg) + modified-release dipyridamole (200 mg) (bd) on serum thromboxane B2 formation and platelet aggregation in healthy volunteers
Investigator:	[redacted]
Study center:	[redacted] Ireland
Publication (reference):	Study has not been published
Clinical phase:	I
Objectives:	To show that the combination of acetylsalicylic acid (25 mg) + modified-release dipyridamole (200 mg) bd is noninferior (within a 4 ng/mL margin) to acetylsalicylic acid (75 mg dispersible tablet once daily) in its effect on inhibition of thromboxane B2 formation
Methodology:	Randomised, open, two-period, crossover trial with washout between treatment periods
No. of subjects entered:	
total:	27
each treatment:	27 acetylsalicylic acid (25 mg) + modified-release dipyridamole (200 mg) 26 acetylsalicylic acid (75 mg)
Diagnosis and main criteria for inclusion:	Male or female healthy volunteers aged 20 to 50 years. Clinically normal medical history and normal findings on physical examination. Capable of comprehending and communicating effectively with the investigator and staff and of providing informed consent. Willing to give informed consent prior to participation in the trial.
Test product:	Combination of acetylsalicylic acid 25 mg and modified-release dipyridamole 200 mg (Asasantin®)
dose:	One capsule bd
mode of admin.:	Oral
batch no.:	907154
Duration of treatment:	Fourteen (± one) days

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Reference therapy:	Acetylsalicylic acid 75 mg dispersible tablet
dose:	75 mg/day
mode of admin.:	Oral
batch no.:	CAY 2
Criteria for evaluation:	
Efficacy:	Serum thromboxane B2, ex-vivo platelet aggregation in response to arachidonic acid (relative to aggregation in response to thrombin receptor activating peptide (TRAP))
Safety:	Adverse events, laboratory evaluations, physical examination, vital signs and electrocardiogram.
Statistical methods:	Analysis of variance using a model suitable for a crossover trial

SUMMARY – CONCLUSIONS:

Efficacy results:

Mean serum thromboxane B2 at day 3 was 10.49 ng/mL (3.23% of baseline value) after Asasantin and 2.08 ng/mL (0.67% of baseline value) after acetylsalicylic acid (75 mg dispersible tablet). There was some additional inhibition of serum thromboxane B2 formation with Asasantin treatment up to fourteen days. In contrast, the effect of acetylsalicylic acid on serum thromboxane B2 formation was fully expressed after three days of treatment.

The 95% confidence interval for the difference between treatments suggests that the effect of Asasantin on serum thromboxane B2 at day 3, day 4 and day 14 is inferior to the effect of acetylsalicylic acid (75 mg dispersible tablet). At day 3, for example, the adjusted mean difference was –8.1 ng/mL (95% confidence interval –15.0, -1.2), significantly less than zero and below the noninferiority margin of –4 ng/mL.

Platelet aggregation (expressed as ratio of aggregation in response to arachidonic acid relative to aggregation in response to TRAP) was reduced from 0.97 to 0.04 after three days of either treatment with no additional inhibition seen during treatment up to fourteen days.

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Safety results:	Twenty-two subjects (81%) experienced transient headache during the Asasantin treatment period compared with three subjects (12%) during the acetylsalicylic acid treatment period. One subject withdrew from the trial because of headache during Asasantin treatment. Other expected side effects of Asasantin or of acetylsalicylic acid (e.g. gastrointestinal events, myalgia) were also observed at lower incidence. No clinically significant haematology, blood biochemistry, 12-lead electrocardiogram or physical examination findings were observed.
Conclusions:	In healthy volunteers, both Asasantin (containing acetylsalicylic acid 25 mg to be taken twice daily) and acetylsalicylic acid (75 mg dispersible tablet) inhibit serum thromboxane B2 formation by at least 96% within three days of starting treatment. The inhibition after Asasantin in this trial was statistically inferior to that after acetylsalicylic acid (75 mg dispersible tablet). The noninferiority of the effect of Asasantin compared to acetylsalicylic acid relative to the 4 ng/mL margin was not established. (The lower limit of the 95% confidence interval for the difference between the treatments was less than –4 ng/mL.) Asasantin and acetylsalicylic acid (75 mg dispersible tablet) are equal and strong inhibitors of platelet aggregation. The inhibition of platelet aggregation is fully expressed by three days of treatment. In healthy volunteers, the therapeutic dose of Asasantin is associated with a high incidence of transient headache. Headache is well tolerated and resolves quickly (often within one day). Expected adverse events for acetylsalicylic acid can be observed in healthy volunteers even in short-term treatment with doses as low as 50 or 75 mg/day.