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***.

3. SYNOPSIS AND TRIAL ABSTRACT

3.1 SYNOPSIS

Name of company: Boehringer Ingelheim		Tabulated Study Report		(For National Authority Use only)
Name of finished product:				
Name of active ingredient: BIBX 245 CL		Page:	Number:	
Ref. to Documentation:	Volume:	Page: to		Addendum No.:
Report date: October 20, 1998	Number: First Draft	Study period (years): May/June 1998		

Title of study:	Single-dose pharmacokinetics of 160 mg BIBX 245 CL and effect of food after oral administration of tablets to healthy subjects (randomized, 2-way-cross-over, open study).
Investigator:	[redacted]
Study centre(s):	Human Pharmacology Center, Boehringer Ingelheim Pharma KG, Biberach / Riss
Publication (reference):	Not yet published
Clinical phase:	I
Objectives:	Investigation of pharmacokinetics and safety
Methodology:	Randomized, 2-way-cross-over, open study, HPLC-MS-MS
No. of subjects entered:	8
total:	8
each treatment:	8
Diagnosis and main criteria for inclusion:	healthy male subjects
Test product:	BIBX 245 CL 80 mg tablets after breakfast
dose:	160 mg
mode of admin.:	p.o.
batch no.:	B980305
Duration of treatment:	single administration
Reference therapy:	BIBX 245 CL 80 mg tablets fasted
dose:	160 mg
mode of admin.:	p.o.
batch no.:	B980305
Criteria for evaluation:	
Efficacy:	Pharmacokinetics: drug plasma concentrations, non-compartmental analysis: C_{max}, $AUC_{0-\infty}$, AUC_{0-t}, t_{max}, λ_z, $t_{1/2}$, MRT_{tot} if possible, pharmacokinetic parameters
Safety:	Adverse events, Laboratory, PR, BP, ECG, post-dose physical examination, global tolerability

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Name of finished product:		SUPPLEMENTARY SHEET		
Name of active ingredient: BIBX 245 CL		Page:	Number:	
Ref. to Documentation:	Volume:	Page: to		Addendum No.:
Report date: October 20, 1998	Number: First Draft	Study period (years): June/July 1998		
Statistical methods:	90 % confidence intervals for pharmacokinetic parameters, descriptive statistics			

SUMMARY - CONCLUSIONS:

Efficacy results:

Pharmacokinetics:

BIBX 245 plasma concentrations were determined by means of a validated mass spectrometric assay (0.10-20 ng/mL, assay precision within 5.6 %, assay accuracy (dev. from theory) within ±12.1 %). BIBB 1216 and BIBB 1230 concentrations in urine were determined by a validated HPLC-UV assay (0.25/0.5-6.0 µg/mL, assay precision within 11.1 % / 6.6 %, assay accuracy (dev. from theory) within ±6.9 % / ±4.6 % for BIBB 1216/1230, respectively.

Mean age of the eight subjects was 28.6 years, their mean weight 73.0 kg and their mean height 180 cm.

The geometric mean amount of the ester BIBX 245 (expressed as % of dose calculated as BIBX 245 BS) excreted in urine as its metabolites BIBB 1216 (alcohol, 23.7 % vs 21.8 %) and BIBB 1230 (N-oxide of the alcohol, 17.4 % vs 18.7 %) was constant for the fed and fasted treatment and averaged 42.8 % and 43.4 % for the fasted and fed treatment, respectively.

Geometric mean (%gCV) BIBX 245 C_{max} values after breakfast (1.61 ng/mL, 76.3 %) was consistently higher in comparison to the fasted treatment (0.356 ng/mL, 29.2 %) and 90 % confidence intervals ranged from 2.84 to 7.24 with a point estimate of 4.54, indicating 4.5 fold higher C_{max} values for the fed treatment. A similar increase was observed for $AUC_{0-\infty}$ (4.81 ng.h/mL, 64.1 % vs 0.966 ng.h/mL, 61.0 %) with 90 % confidence intervals ranging from 3.88 to 6.38 with a point estimate of 4.98. This indicates a five-fold increase in bioavailability of BIBX 245, if the drug is administered with a light breakfast.

A comparison of AUC data for the tablet with those from the capsule (fed: 4.81 ng.h/mL vs 2.51 ng.h/mL in six volunteers of trial 537.3) suggested a probably even higher bioavailability for the tablet in comparison to the capsule. Capsule and tablet were studied with different volunteers using an identical trial design. However, the higher values for the tablet should be considered with care due to the nonlinear pharmacokinetics of BIBX 245.

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Results of the non-compartmental pharmacokinetic evaluation (n=8).

		160 mg BIBX 245 CL: fed				160 mg BIBX 245 CL: fasted				90%CI
		gmean	% gCV	a.mean	% CV	gmean	% gCV	a.mean	% CV	
C_{max}	[ng/mL]	1.61	76.3	2.00	74.1	0.356	29.2	0.369	27.9	2.84 - 7.24
t_{max}	[h]	#1.25	§0.5-3	1.5	53.5	#1.0	§0.5-1.5	1.1	39.3	--
$AUC_{0-\infty}$	[ng·h/mL]	4.81	64.1	5.60	60.5	0.966	61.0	1.10	51.5	3.88 - 6.38
$t_{½}$	[h]	1.7	36.2	1.8	35.1	1.5	56.0	1.7	53.6	0.808 - 1.59
MRT_{tot}	[h]	3.44	42.7	3.69	39.3	2.77	45.5	3.01	43.9	0.900 - 1.70
Ae_{ss} 1216	[%]	23.7	61.3	26.9	49.1	21.8	74.2	26.6	75.2	
Ae_{ss} 1230	[%]	17.4	32.3	18.1	24.9	18.7	24.0	19.2	20.7	
$Ae_{ss\ sum}$	[%]	43.4	28.3	45.0	28.6	42.8	38.6	45.8	45.3	

#: median, §: range, gmean: geometric mean, a-mean: arithmetic mean, Ae_{ss} 1216/1230: amount of BIBX excreted as its metabolite BIBB 1216 or BIBB 1230 calculated as BIBX 245 sum: sum of both metabolites.

Safety results:
Only unspecific adverse events were reported. Most subjects reported headache during the trial, in one case associated with vomiting, in another with dizziness. All subjects recovered spontaneously.

Conclusions:
The bioavailability of BIBX 245 increased fivefold when administered with a light breakfast. A historical comparison revealed a similar or even higher bioavailability of the BIBX 245 CL tablets 80 mg compared to BIBX 245 CL capsules 80 mg. Apart from unspecific adverse events which the test drug was well tolerated.