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:				
Name of active ingredient: Ibuprofen		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 04 JUL 2003	**Number:** U03-0055	**Study period (years):** 08/2002 – 10/2002		

Title of study:	Open-label, randomised, single dose, four-way crossover study to investigate the relative bioavailability of a 400 mg ibuprofen extrudate tablet compared to a 400 mg ibuprofen lysinate tablet (Dolormin extra®) and a 400 mg ibuprofen tablet (Brufen® 400 mg, Denmark) in fasted condition and after ingestion of a standardised meal in healthy male and female volunteers.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim
Publication (reference):	No
Clinical phase:	I
Objectives:	To demonstrate average bioequivalence between a 400 mg ibuprofen extrudate tablet (Test) and a 400 mg ibuprofen lysinate tablet (Dolormin extra ®; reference 1) under fasted conditions. To determine the relative bioavailability of ibuprofen following single administration of a 400 mg ibuprofen extrudate tablet (Test) compared to a 400 mg ibuprofen tablet (Brufen® 400mg, Denmark; Reference 2) under fasted conditions. To determine the relative bioavailability of ibuprofen following single administration of a 400 mg ibuprofen extrudate tablet (Test) compared to a 400 mg ibuprofen lysinate tablet (Dolormin extra ®; reference 1) or a 400 mg ibuprofen tablet (Brufen® 400mg, Denmark; Reference 2), respectively, under fed conditions. To evaluate the effect of food on the pharmacokinetics of ibuprofen for all three formulations.
Methodology:	Open-label, randomised, twelve-sequence, four-period, single centre, single dose, crossover design.
No. of subjects:	
total:	36 subjects, 18 male and 18 female
each treatment:	Ibuprofen extrudate, each fed and fasted: 24 Dolormin extra® (Reference 1), each fed and fasted: 24 Brufen® 400 mg, Denmark (Reference 2), each fed and fasted: 24

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Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age 21 – 50 years, BMI range: 18.5 to 29 kg/m2
Test product:	Ibuprofen extrudate tablet
dose:	400 mg
mode of admin.:	Peroral administration after an overnight fast / standardised breakfast with 240 mL water
batch no.:	1E0401A0
Duration of treatment:	One day (single administration) for each treatment
Reference therapy:	Ibuprofen lysinate tablet [Dolormin extra®] (Reference 1) Ibuprofen tablet [Brufen® 400 mg, Denmark] (Reference 2)
dose:	400 mg
mode of admin.:	Peroral administration after an overnight fast / after a standardised breakfast with 240 mL water
batch no.:	Reference 1: K020705 = 01LL416 Woelm Pharma Reference 2: K020706 = 1028 Knoll
Duration of treatment:	One day (single administration) for each treatment
Criteria for evaluation:	
Pharmacokinetics:	Primary endpoints: C_{max}, AUC_{0-tz}, $AUC_{0-\infty}$ Secondary endpoints: individual time courses of the ibuprofen plasma concentrations, AUC_{trunc}, t_{max}, $t_{1/2}$, λ_z, MRT_{tot}, CL/F, V_z/F
Safety:	Clinical examination including physical examination, vital signs; ECG, laboratory tests, adverse events
Statistical methods:	The two-sided 90% confidence intervals (CIs) for expected median intra-subject (intra-individual) ratios of C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ were contained in the range of 80-125%. The statistical model was ANOVA on log transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". CIs were to be based on the residual error from ANOVA. Additionally, the corresponding point estimates for C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$ were provided. Descriptive statistics were performed for all other parameters.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Ibuprofen plasma concentrations were determined by a specific and validated HPLC assay (0.25 - 50 µg/mL) with UV-detection. Assay precision and assay accuracy were within 2.9% and ± 2.7%. Mean age of the 38 subjects was 32 years, the mean body weight 71 kg (females 65 kg, males 77 kg).

Geometric means (gCV %) of primary endpoints of the pharmacokinetic analysis as well as the values for t_{max} are shown in Table 2.1 below.

Table 2.1.: Pharmacokinetic Parameters

IP 1024.5		**400 mg extrudate**		**400 mg lysinate**		**400 mg Brufen®**	
		fed	**fasted**	**fed**	**fasted**	**fed**	**fasted**
Parameter		N = 24	N = 24	N = 25	N = 24	N = 24	N = 24
C_{max} [µg/mL]	gMean	26.2	41.1	29.6	41.2	26.0	33.5
	gCV (%)	26.0	21.3	17.4	16.0	27.6	17.8
t_{max} [h]	median	1.25	0.75	1.5	0.75	1.63	1.38
	range	1.0 - 5.0	0.5 - 1.5	1.0 - 3.0	0.5 - 1.5	0.75 - 4.0	0.5 - 4.0
AUC_{0-oo} [µg*h/mL]	gMean	91.9	111	97.9	112	92.1	117
	gCV (%)	18.9	19.1	18.0	17.8	17.0	17.8
AUC_{0-tz} [µg*h/mL]	gMean	89.8	109	95.7	110	89.9	114
	gCV (%)	18.6	18.6	17.3	17.1	16.7	17.3

Source data: Appendix 16.3.2, Tables 16.3.2: 7 to 12

Test for bioequivalence between 400 mg ibuprofen extrudate tablet and 400 mg ibuprofen lysinate tablet (Dolormin extra®):

Ninety percent confidence intervals for all primary PK parameter were completely included in the interval 80.0 % to 125.0 % (C_{max}: 88.61 % - 105.19 %; $AUC_{0-\infty}$: 93.39 % - 103.41 %; AUC_{0-tz}: 93.62 % - 103.41 %). Bioequivalence at fasted conditions between the ibuprofen extrudate tablet and the ibuprofen lysinate tablet (Dolormin extra®) can be concluded.

Safety results:

Treatment with 400 mg ibuprofen as extrudate tablet formulation, as lysinate tablet formulation, and as Brufen® tablet, with and without food, was safe and well tolerated. The overall number of adverse events was low. No difference between treatments in adverse event frequency could be observed. An episode of acute gastritis in one subject during wash-out after ibuprofen lysinate administration was classified as serious, drug-related adverse event. However, gastrointestinal adverse reactions, especially gastric mucosal damage, are well known to occur with all non-steroidal anti-inflammatory drugs. No other

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adverse events were considered to be drug-related. A total of four adverse events were seen in the MedDRA System Organ Classes Gastrointestinal disorders. No more than two adverse events were reported in any of the other System Organ Classes. There were no relevant changes in vital signs, ECG, and laboratory analyses.

Conclusions:

Bioequivalence between the 400 mg ibuprofen extrudate tablet and the 400 mg ibuprofen lysinate tablet (Dolormin extra®) - either given fasted or fed, respectively - was confirmed. Thus, both formulations are considered as inter-changeable.

Taking into account the respective dietary condition (fed vs. fed or fasted vs. fasted, respectively), the overall extent of ibuprofen absorption was almost identical for all three investigated preparations (ibuprofen extrudate tablet; Dolormin extra®; Brufen®).

Rate of absorption at fasted state was considerably faster following administration of the ibuprofen extrudate and the ibuprofen lysinate tablet than for Brufen®. This obvious difference between the extrudate tablet (or lysinate tablet, respectively) and Brufen® - with regard to rate of absorption - is entirely blunted by food intake.

A food effect, i.e. a significant decrease with regard to rate and extent of absorption, was observed for all three investigated ibuprofen formulations.

Treatment with 400 mg ibuprofen as extrudate tablet formulation, with and without food, was safe and well tolerated. The overall number of adverse events was low. No relevant differences between treatments (ibuprofen extrudate versus ibuprofen lysinate versus “conventional” ibuprofen) could be observed. There were no relevant changes in vital signs, ECG, and laboratory analyses.