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**		
Name of finished product: MicardisPlus®				
Name of active ingredient: Telmisartan + Hydrochlorothiazide		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 23 March 2005	**Number:** U04-1571	**Study period (dates):** 28 APR 03 - 08 AUG 03		

Title of study:	Relative bioavailability of telmisartan and HCTZ p.o. (80 mg telmisartan/12.5 mg HCTZ) in two experimental formulations (given t.i.d. for one day each) compared to the standard formulation 80 mg telmisartan/12.5 mg HCTZ (MicardisPlus®), given t.i.d. for one day in healthy female and male subjects. A three-way crossover, open, randomised study.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, D-88397 Biberach/Riss
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	To assess the comparative pharmacokinetics of telmisartan/HCTZ in two new formulations based on sodium salt compared to the present commercial formulation (MicardisPlus®).
Methodology:	Randomised, open label, three-way crossover pharmacokinetic study with six treatment sequences
No. of subjects:	
planned:	24
actual:	entered: 24 enrolled: 45 Treatment A: Direct compressible formulation based on sodium salt; tablet (DC) entered: 24 treated: 24 analysed (for primary endpoint): 24 Treatment B: Dry granulated formulation based on sodium salt; tablet (DG) entered: 24 treated: 24 analysed (for primary endpoint): 24 Treatment C: Commercial formulation (MicardisPlus®): entered: 24 treated: 23 analysed (for primary endpoint): 22
Diagnosis and main criteria for inclusion:	Healthy female and male subjects, age 18-55 years, BMI $\geq$18.5 and $\leq$29.9 kg/m^2 with no relevant disease
Test product:	Telmisartan /HCTZ (two new formulations based on sodium salt as compression tablet (DC) or dry granulation tablet (DG)),
dose:	80 mg Telmisartan/12.5 mg HCTZ, t.i.d. for one day for each formulation
mode of admin.:	per os

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batch no.:	Telmisartan /HCTZ direct compression tablet: B030208 (BIBR 277NA TA 99 1A 1A) Telmisartan /HCTZ dry granulation tablet: B030302 (BIBR 277NA TA 99 1B 1A)
Duration of treatment:	3 days
Reference therapy:	MicardisPlus® (present commercial formulation)
dose:	80 mg telmisartan/ 12.5mg HCTZ, t.i.d. for one day
mode of admin.:	per os
batch no.:	207595 (BIBR 277SE TA 18H 1A)
Criteria for evaluation:	
Efficacy:	Efficacy endpoints were not evaluated. Assessment of $AUC_{0\text{-inf.}}$ and C_{max} for telmisartan and HCTZ and $\%Ae_{0\text{-}48h}$ of HCTZ of each treatment as primary endpoints. Assessment of t_{max}, $t_{1/2}$, CL_{tot}/F, MRT_{tot}, V_z/F as secondary endpoints.
Safety:	Adverse events, laboratory tests, vital signs, 12-lead ECG, assessment of tolerability
Statistical methods:	Two-sided 90 % confidence intervals for test/reference ratios for $AUC_{0\text{-}\infty}$ and C_{max}, descriptive statistics
SUMMARY – CONCLUSIONS:	
Efficacy results:	This trial was an open-label, three period randomised crossover pharmacokinetic study with 6 sequences, each treatment given t.i.d. for one day. Twenty-four female and male subjects entered the trial. The study was divided into a screening period and three treatment periods with a two-week washout between treatments. Pharmacokinetic results: The geometric mean area under the plasma concentration time curves, $AUC_{0\text{-inf.}}$ of telmisartan of the commercial tablet formulation (CF), the dry granulation tablet (DG), and the direct compression tablet (DC) were 2850, 2660 and 2680 ng*h/mL, respectively. The geometric coefficient of variation, gCV was 64 – 68 %. The geometric mean maximum plasma concentrations, C_{max} of the commercial tablet formulation, the dry granulation tablet, and the direct compression tablet were 359, 300 and 272 ng/mL, respectively. Two-sided 90 % confidence intervals for test/reference ratios for $AUC_{0\text{-}\infty}$ and C_{max} of telmisartan are shown in the table below:

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Parameter	Test (N=24)	Reference (N=22)	Adjusted Mean Ratio	Two sided 90 % Confidence Interval	
				Lower limit	Upper limit
	Tablet	Tablet			
$AUC_{0-\infty}$	DC (*1)	CF (*3)	0.928	0.835	1.031
$AUC_{0-\infty}$	DG (*2)	CF (*3)	0.912	0.818	1.018
C_{max}	DC	CF	0.772	0.650	0.916
C_{max}	DG	CF	0.852	0.718	1.012

(*1): N=23, (*2): N=22, (*3): N=20

The confidence interval limits for $AUC_{0-inf.}$ (denoted $AUC_{0-\infty}$) of the direct compression and dry granulation tablet were within the bioequivalence acceptance limits of 0.8 – 1.25. However, no bioequivalence was demonstrated for C_{max} of both experimental formulations. The $AUC_{0-inf.}$ of HCTZ were similar for all three formulations with 1300 – 1350 ng*h/ml. The same was the case for the geometric mean C_{max} of HCTZ which was in the range of 113 – 120 ng/mL. Interindividual variability of HCTZ pharmacokinetic parameters was low. The geometric coefficient of variation of the geom. mean of the $AUC_{0-inf.}$ was 19 – 21 %. With regard to HCTZ pharmacokinetic parameters, the experimental tablet formulations were bioequivalent with the commercial tablet.

Safety results:

The global clinical assessments of 52 of 72 possible treatment periods of all subjects were good, 17 were satisfactory and one was not satisfactory (direct compression tablet). The tolerability of the present commercial formulation was not assessable in 2 subjects in this trial due to a severe adverse event (sports accident) respectively an adverse event (gastrointestinal illness). Both events were not related to the trial medication. No relevant safety problems concerning vital signs, ECG, physical examination and clinical laboratory safety test results occurred. Eighteen (11 female and 7 male) of 24 subjects reported a total of 53 adverse events during the whole trial including washout periods. From all adverse events the following were considered to be related to the trial medication: nervous system disorders like headache (22) and dizziness (3); gastrointestinal disorders like diarrhoea (4), loose stools (1), nausea (2), vomiting (2) and abdominal rigidity (1); general disorders like fatigue (1) as well as musculoskeletal and connective tissue disorder like myalgia (1). All these adverse events have been reported in some way in previous clinical trials and are

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	listed accordingly in the product information. Those events which were judged to be not related to the trial medication (16) included headache, dizziness, diarrhoea, vomiting, nausea, renal pain, back pain, pharyngolaryngeal pain, seasonal allergy, rhinitis and influenza like illness. One serious adverse event occurred during the second wash out phase which was considered to be not related to the medication. The subject discontinued prematurely because of a sports accident that had led to a broken elbow with the need of surgery intervention and hospitalisation.
Conclusions:	Regarding the $AUC_{0\text{-inf.}}$ of telmisartan of the direct compression and dry granulation tablet bioequivalence could be shown. However, no bioequivalence was demonstrated for C_{max} of both experimental formulations. The $AUC_{0\text{-inf.}}$ of HCTZ was similar for all three formulations. No major safety problems occurred during the study which could be related to the treatment with the two experimental formulations of telmisartan/hydrochlorothiazide based on sodium salt or of the present commercial formulation MicardisPlus®.