Clinical Study Synopsis for Public Disclosure

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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: Micardis® Plus				
Name of active ingredient: BIBR 277 HCT, telmisartan + hydrochlorothiazide		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 15 March 2006	**Number:** U06-3139	**Study period (dates):** 07 August 2005 – 11 October 2005		

Title of study:	Bioequivalence of 80 mg telmisartan/12.5 mg HCTZ fixed dose combination compared with its monocomponents in healthy male volunteers II (an open-label, randomised, single-dose, two-sequence, four-period replicated crossover study)
Investigator:	[redacted]
Study center:	[redacted] Japan
Publication (reference):	Data of this study has not been published.
Clinical phase:	I
Objectives:	To demonstrate the bioequivalence of 80 mg telmisartan/12.5 mg HCTZ fixed dose combination compared with its monocomponents.
Methodology:	Open label, randomised, single dose, two sequence, four period, replicated crossover design
No. of subjects:	
planned:	entered: 68
actual:	enrolled: 70 Treatment sequence 1: (fixed dose combination → monocomponents (two individual products) → monocomponents → fixed dose combination) entered: 34 treated: 34 Treatment sequence 2: (monocomponents (two individual products) → fixed dose combination → fixed dose combination → monocomponents) entered: 34 treated: 34 Analysed for bioequivalence of telmisartan 80 mg as a fixed dose combination in comparison with the monocomponent: 34 Analysed for bioequivalence of HCTZ 12.5 mg as a fixed dose combination in comparison with the monocomponent: 34
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥ 20 and ≤ 35 years, body weight ≥ 50 kg, body mass index (BMI) range: ≥ 17.6 and ≤ 25.0 kg/m^2

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Test product:	Fixed dose combination tablet of telmisartan and hydrochlorothiazide (HCTZ)
dose:	Telmisartan 80 mg/HCTZ 12.5 mg
mode of admin.:	Oral administration after an overnight fast of at least 10 hours, with 150 mL water
batch no.:	B04115
Duration of treatment:	Single-dose during each treatment period with sampling for 72 hours followed by at least 2-week washout period between treatments
Reference therapy:	Telmisartan tablet and HCTZ tablet
dose:	Telmisartan 80 mg, HCTZ 12.5 mg
mode of admin.:	Oral administration after an overnight fast of at least 10 hours, with 150 mL water
batch no.:	Telmisartan tablet: 401508, HCTZ tablet: B03026
Criteria for evaluation:	
Pharmacokinetics:	Pharmacokinetics primary endpoints: AUC_{0-tz}, and C_{max} secondary endpoints: $AUC_{0-\infty}$, t_{max}, λ_z, $t_{1/2}$, MRT_{po}
Safety:	Physical examination, vital signs (blood pressure, plus rate), electrocardiogram (ECG), laboratory tests, adverse events
Statistical methods:	The pharmacokinetic parameters of telmisartan and HCTZ were evaluated separately. The two-sided 90% confidence intervals (CIs) for the intra-subject ratio (as estimated by the geometric mean of the ratio) of AUC_{0-tz} and C_{max} were calculated to determine whether the CIs were within the acceptance range of 80-125% for bioequivalence and the corresponding point estimators (geometric means) for the median intra-subject ratios were provided.

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Statistical methods: (cont.)	For telmisartan, based on a four-period replicated crossover design, the statistical analysis was an analysis using a mixed-effect model on log-transformed parameters including 'sequence', 'period' and 'treatment' as fixed effect and 'subject within sequence' as random effect in the model. The difference between test and reference means was estimated using the restricted maximum likelihood (REML) method. Whereas for HCTZ, based on a standard two-way crossover design, the statistical analysis was using an analysis of variance (ANOVA) model including the same effects as in the model for telmisartan. The difference between test and reference means was estimated using the least square method. For all non-categorical parameters, descriptive statistics were calculated. For all categorical parameters, frequency was tabulated.

SUMMARY – CONCLUSIONS:

Pharmacokinetic results:

Assessment of bioequivalence (Telmisartan)

The ratios of the adjusted gMean values of C_{max} and AUC_{0-tz} of fixed dose combination to those of monocomponents were 1.008 and 0.990, respectively. The degrees of intra-individual variability of C_{max} were 50.8% for fixed dose combination and 40.6% for monocomponents. Those of AUC_{0-tz} were 15.7% for fixed dose combination and 14.7% for monocomponents. The 90% CIs were from 91.9 to 110.5% for C_{max} and from 96.0% to 102.2% for AUC_{0-tz}. The 90% CIs for C_{max} and AUC_{0-tz} of telmisartan were within the acceptance range (80-125%).

Assessment of bioequivalence (HCTZ)

The ratios of the adjusted gMean values of C_{max} and AUC_{0-tz} of fixed dose combination to those of monocomponents were 0.911 and 0.959, respectively. The degrees of intra-individual variability of C_{max} and AUC_{0-tz} calculated from the mean square errors were 15.0% and 11.2%, respectively. The 90% CIs were from 87.2% to 95.1% for C_{max} and from 92.8% to 99.0% for AUC_{0-tz}. The 90% CIs for C_{max} and AUC_{0-tz} were within the acceptance range (80-125%).

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Safety results:

Of 68 subjects received at least one dose of the study drug, 14 subjects (20.6%) experienced adverse events. The intensity of the adverse events was mild and any treatment for the events was not required. Serious adverse events were not reported.

Adverse events associated with blood pressure-lowering effect were frequently reported. Dizziness postural was reported in 2 subjects (3.0%), orthostatic hypotension in 1 subject (1.5%) and fatigue caused by decrease of blood pressure in 1 subject (1.5%) during treatment with fixed dose combination. Dizziness postural was reported in 2 subjects (3.0%) and tachycardia in 1 subject (1.5%) during treatment with monocomponents.

Telmisartan and HCTZ (fixed dose combination and monocomponents) decreased diastolic and systolic blood pressure by approximately 8 mmHg and 7 mmHg, and increased pulse rate by approximately 12 bpm 8 hours after administration. Nevertheless, the intensity of the adverse events associated with blood pressure-lowering effect was mild.

Conclusions:

The results of analyses for both telmisartan and HCTZ met the bioequivalence criteria, and thus fixed dose combination and monocomponents of telmisartan 80 mg and HCTZ 12.5 mg were proven to be bioequivalent.

Fixed dose combination and monocomponents of telmisartan 80 mg and HCTZ 12.5 mg were well tolerated in healthy subjects.