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: MICARDIS® PLUS				
Name of active ingredient: BIBR 277 HCT, telmisartan + hydrochlorothiazide		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 11 March 2005	**Number:** U05-3037	**Study period (dates):** 9 September 2004 – 1 October 2004		

Title of study:	Bioequivalence of 40 mg telmisartan / 12.5 mg HCTZ of fixed dose combination compared to its monocomponents in healthy male volunteers (an open-label, randomised, single-dose, two-way crossover study)
Investigator:	[redacted]
Study center:	[redacted] Japan
Publication (reference):	Data of this study has not been published.
Clinical phase:	I
Objectives:	To establish the bioequivalence of fixed dose combination of 40 mg telmisartan / 12.5 mg HCTZ vs. its monocomponents
Methodology:	Open-label, randomised, single-dose, two-way crossover design
No. of subjects:	
planned:	entered: 30
actual:	enrolled: 30 (all subjects received both 40 mg telmisartan / 12.5 mg HCTZ fixed dose combination and its monocomponents fixed dose combination of 40 mg telmisartan / 12.5 mg HCTZ followed by its monocomponents: entered: 15 treated: 15 analysed (for pharmacokinetics and safety): 15 monocomponents of 40 mg telmisartan and 12.5 mg HCTZ followed by the fixed dose combination : entered: 15 treated: 15 analysed (for pharmacokinetics and safety): 15
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age: ≥ 20 and ≤ 35 years, BMI range: ≥ 17.6 and ≤ 25.0 kg/m²
Test product:	Telmisartan and HCTZ, fixed dose combination tablet
dose:	40 mg telmisartan / 12.5 mg HCTZ
mode of admin.:	Oral administration after an overnight fast of at least 10 hours, with 150 mL water
batch no.:	B04084

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Duration of treatment:	1 day for each treatment
Reference therapy:	Telmisartan tablet and HCTZ tablet
dose:	40 mg telmisartan and 12.5 mg HCTZ
mode of admin.:	Oral administration after an overnight fast of at least 10 hours, with 150 mL water
batch no.:	Telmisartan / 106505 and HCTZ / B03026
Criteria for evaluation:	
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 (BP, PR), ECG, laboratory tests, adverse events
Statistical methods:	Pharmacokinetic parameters of telmisartan and HCTZ were evaluated separately. Two-sided 90% Confidence intervals (CIs) for the intra-subject ratio (as estimated by the geometric mean of the ration) of AUC_{0-tz} and C_{max} were calculated to determine whether the CIs are contained in the acceptance range of 80-125% for bioequivalence. Additionally, the corresponding point estimators (geometric means) for the median intra-subject ratios were provided. The statistical model was ANOVA on log transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". The CIs were based on the residual error from ANOVA. Descriptive statistics for all other parameters were calculated. Frequencies were tabulated for all categorical parameters.

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SUMMARY – CONCLUSIONS:

Pharmacokinetic results:

Assessment of bioequivalence (Telmisartan)

The ratios of the adjusted mean values of C_{max} and AUC_{0-tz} of fixed dose combination to those of monocomponents were 0.895 and 0.988, respectively. The degrees of intra-individual variability of C_{max} and AUC_{0-tz} calculated from the mean square errors were 25.6% and 13.1%, respectively. The 90% confidence intervals (CIs) were from 80.2% to 100.0% for C_{max} and from 93.3% to 104.7% for AUC_{0-tz}, respectively. 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 mean values of C_{max} and AUC_{0-tz} of fixed dose combination to those of monocomponents were 0.891 and 0.945, respectively. The degrees of intra-individual variability of C_{max} and AUC_{0-tz} calculated from the mean square errors were 14.4% and 11.0%, respectively. The 90% CIs were from 83.6% to 94.9% for C_{max} and from 90.0% to 99.1% for AUC_{0-tz}, respectively. Although the upper limits of the 90% CIs for C_{max} and AUC_{0-tz} of HCTZ were slightly lower than unity, the 90% CIs for C_{max} and AUC_{0-tz} were within the acceptance range (80-125%).

Safety results:

There were 2 adverse events related to the study drug treatment: hypotension in 1 subject and heart rate increased in 1 subject. These adverse events were, however, mild and transient, and the subjects recovered without treatment. No serious adverse event occurred.

Conclusions:

The results of analysis for both telmisartan and HCTZ met the bioequivalence criteria, and thus fixed dose combination and monocomponents of telmisartan 40 mg and HCTZ 12.5 mg were proven to be bioequivalent.

Telmisartan 40 mg and HCTZ 12.5 mg, which were concomitantly administered either in fixed dose combination or in monocomponents to healthy subjects, were well tolerated in this clinical study. There was no difference in safety between fixed dose combination and its monocomponents.