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***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim Pharma KG		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Telmisartan				
Name of active ingredient: BIBR 277 SE		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 24 March 2000	**Number:** 502.324	**Study period (years):** Oct. 1999 - Dec. 1999		

Title of study:	Relative oral bioavailability of 40 mg Telmisartan / 12.5 mg HCTZ fixed dose combination compared with its monocomponents in healthy subjects. A 4 period cross-over, open, randomized, replicate design study.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre, Biberach
Publication (reference):	not yet published
Clinical phase:	I
Objectives:	To demonstrate bioequivalence of Telmisartan and HCTZ administered as fixed dose combination in comparison to the single dose unit formulations.
Methodology:	Open-label, randomized, four way cross-over replicate design
No. of subjects entered:	
total:	32 (16 female and 16 male)
each treatment:	32
Diagnosis and main criteria for inclusion:	healthy male and female subjects 18 to 55 years of age
Test product:	Telmisartan and HCTZ, fixed combination oblong tablet
dose:	40 mg Telmisartan / 12.5 mg HCTZ
mode of admin.:	oral
batch no.:	902840
Duration of treatment:	Single-dose during each treatment period with sampling for 72 hours followed by a 2 week washout period between treatments
Reference therapy:	Telmisartan, oblong tablet and separate HCTZ tablet
dose:	40 mg (Telmisartan) and 12.5 mg (HCTZ)
mode of admin.:	oral
batch no.:	901840 (Telmisartan) and F4836 (HCTZ)
Criteria for evaluation:	Timed plasma concentration determination of Telmisartan and HCTZ following single dosing, urinary excretion of HCTZ
Efficacy:	not applicable
Safety:	Adverse events, tolerability, routine laboratory, pulse rate, blood pressure, ECG
Statistical methods:	descriptive statistics, average, average scaled, and individual bioequivalence

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SUMMARY - CONCLUSIONS:

This trial was a single dose, open-label, 4 period randomized crossover pharmacokinetic study of replicate design with 2 sequences: ABAB and BABA (B = reference = individual tablets; A = test = fixed dose combination). Thirty-two healthy male and female Caucasian subjects entered the trial. The study was divided into a screening period and four treatment periods with a two-week washout between treatments.

Primary parameters for the assessment of average bioequivalence of HCTZ were AUC, C_{max} and $A_{e(0-48)}$. A multiplicative model using logarithmically transformed parameter values was used for the analysis of variance (ANOVA). The effects treatment, period, sequence and subject within sequence were included in the ANOVA model. The shortest 90 % confidence intervals for the ratio of the primary endpoints were calculated. Bioequivalence of the Telmisartan pharmacokinetic parameters AUC and C_{max} was assessed by a moment based, scaled criterion M_{as} for average scaled bioequivalence. A one sided 95 % confidence interval for the moment based scaled measure M_{as} was calculated using the percentile bootstrap method. Bioequivalence was to be accepted if the transformed upper bound of the 95 % confidence interval for M_{as} on the ratio scale, was less than or equal to 125 %.

Assessment of average bioequivalence of HCTZ:
The 90 % confidence intervals for the "test/reference" mean ratio for the primary pharmacokinetic variables $AUC_{0-\infty}$ and C_{max} are 94.6 % to 107.1 % and 99.7 % to 115.1 %, respectively. The confidence intervals for the "test/reference" mean ratio of the pharmacokinetic variable A_{e0-48h} is 93.2 % to 103.2 %. All confidence intervals fall in the bioequivalence range of 80 % to 125 %.

Assessment of average scaled bioequivalence of Telmisartan:
The upper bounds of the one-sided 95 % confidence interval for the average, scaled bioequivalence measure M_{as} are, on the ratio scale, 107.7 % and 116.5 % for the primary pharmacokinetic variables $AUC_{0-\infty}$ and C_{max}, respectively. These upper bounds of the confidence intervals are below the upper bound of the bioequivalence range, 125 %. Thus average, scaled bioequivalence with respect to the variables $AUC_{0-\infty}$ and C_{max} is shown.

Safety results

Tolerability was rated as good in all cases. Fourteen of the 32 subjects reported a total of 23 adverse events. These events included 8 episodes of headache, 3 episodes of upper respiratory tract infection, one episode of thrombophlebitis, vomiting, neurosis, tooth disorder, rash erythematous, haematoma, accident vehicular, dizziness, dermatitis fungal, pharyngitis, arrhythmia atrial and epistaxis. All of the episodes were mild to moderate in intensity. There was no serious adverse event. One subject discontinued prematurely because of the adverse event accident vehicular. There was no reasonable causal relationship between the above listed adverse events and the test drug. There were no relevant changes in vital signs, laboratory parameters, ECG and physical examination between baseline and post-examination.

Conclusions

Bioequivalence between the test (fixed dose combination) and reference (individual, separate tablets) treatments in this study has been shown with respect to both primary and secondary pharmacokinetic characteristics of both Telmisartan and HCTZ. The treatments were well tolerated.