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***.

3. SYNOPSIS AND STUDY ABSTRACT

3.1 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: Telmisartan / Hydrochlorothiazide		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: March 15, 1999	**Number:** 502.136	**Study period (years):** Sept./Oct. 1998		

Title of study:	Relative oral bioavailability of 80 mg telmisartan / 12.5 mg HCTZ fixed dose combination compared with its monocomponents in healthy subjects. A 4 period cross-over, open, randomised, replicate design study.
Investigators:	[redacted]
Authors:	[redacted]
Study centre(s):	Human Pharmacology Centre, Biberach
Publication(reference):	not yet published
Clinical phase:	I
Objectives:	To demonstrate the bioequivalence of telmisartan and HCTZ administered as fixed dose combination in comparison to the single unit formulations
Methodology:	Open-label, randomised, four way cross-over replicate design
No. of subjects:	
total:	20 (10 female and 10 male)
each treatment:	20
Diagnosis and main criteria for inclusion:	Healthy male and female Caucasian subjects 18 to 45 years of age
Test product:	Telmisartan and HCTZ, fixed combination oblong tablet
dose:	80 mg telmisartan / 12.5 mg HCTZ
mode of admin.:	oral
batch no.:	9960236
Duration of treatment:	Single-dose during each treatment period with sampling for 96 hours followed by a 2 week washout period between treatments
Reference therapy:	Telmisartan, oblong tablet and a separate HCTZ tablet
dose:	80mg (telmisartan) and 12.5 mg (HCTZ)
mode of admin.:	oral
batch no.:	9960325 (telmisartan) and F4260 (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, PR, BP

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Statistical methods:
Descriptive statistics, average, average scaled and individual bioequivalence

Summary - Conclusions:
This trial was a single dose, open-label, 4 period randomised crossover pharmacokinetic study of replicate design with 2 sequences: RTTR and TRRT (R = reference = individual tablets; T=test = fixed dose combination). Twenty 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 $Ae_{(0-48)}$. 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}. 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 upper bound of the 95% confidence was less than or equal to the constant $\Delta_{ms}^2 = 0.20^2$.

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 91.8% to 109.5% and 90.8% to 107.4%, respectively. The confidence intervals for the "test/reference" mean ratio of the pharmacokinetic variable Ae_{0-48h} is 91.0% to 103.9%. 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, 109.4% and 113.8 % 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. There was no change in heart rate. Fourteen of 20 subjects reported a collective total of 25 episodes of adverse reactions: 14 episodes headache, 4 episodes upper respiratory tract infection, 2 episodes back pain, 2 episodes rash, 1 episode dysmenorrhea, 1 episode pharyngitis. Only the rash in the one subject in temporal association with both poly and monocomponent therapy was considered drug related. Except for one episode of back pain, one episode of dysmenorrhea, one upper respiratory tract infection, and one headache, all adverse reactions had a severity of mild or moderate. There was no concomitant therapy required and recovery was spontaneous in all. There was no association between treatment group and reaction.

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.