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: Telmisartan (Micardis)				
Name of active ingredient: Telmisartan 80 mg		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 16 March 2005	**Number:** U04-2097	**Study period (dates):** 02 APR 04 - 19 MAY 04		

Title of study:	Relative bioavailability of telmisartan and SR26334, the main metabolite of clopidogrel, after co-administration compared to the bioavailability of telmisartan and SR26334 after p.o. administration of 80 mg telmisartan and 75 mg clopidogrel alone. A four-way, single dose, open, randomised crossover study in 24 healthy male and female subjects
Investigator:	[redacted]
Study center(s):	[redacted] Germany
Publication (reference):	-
Clinical phase:	I
Objectives:	To investigate the relative biovailability of SR26334 respectively of telmisartan after concomitant administration of 75 mg clopidogrel and 80 mg telmisartan (Test 1) relative to SR26334 administered as 75 mg clopidogrel alone (Reference 1), respectively relative to 80 mg telmisartan alone (Reference 2) To investigate the relative biovailability of SR26334 respectively of telmisartan administered as 75 mg clopidogrel 30 minutes after intake of 80 mg telmisartan (Test 2) relative to SR26334 administered as 75 mg clopidogrel alone (Reference 1), respectively relative to 80 mg telmisartan alone (Reference 2)
Methodology:	Randomised, open label, 4-way crossover trial, 4 treatment sequences
No. of subjects:	
planned:	entered:24
actual:	enrolled: 24
Diagnosis and main criteria for inclusion:	Healthy female and male subjects, age $\geq$ 40 years, BMI $\geq$18.5 and $\leq$29.9 kg/m^2
Test product:	Telmisartan plus Clopidogrel
dose:	80 mg plus 75 mg
mode of admin.:	p.o.
batch no.:	206065 (Telmisartan), K040227=300193 (Plavix, Clopidogrel)
Duration of treatment:	One day per treatment, total: 4 days
Reference therapy:	Telmisartan or Clopidogrel alone
dose:	80 mg or 75 mg

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mode of admin.:	p.o.
batch no.:	206065 (Telmisartan), K040227=300193 (Plavix, Clopidogrel)
Criteria for evaluation:	
Efficacy:	$AUC_{0-\infty}$, C_{max}, t_{max} of telmisartan and SR26334
Safety:	Adverse events, laboratory tests, ECG, vital signs
Statistical methods:	Two-sided 90 % confidence intervals for test/reference ratios for $AUC_{0-\infty}$ and C_{max}, descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy results:
Pharmacokinetics:

The geometric mean $AUC_{0-\infty}$ of telmisartan after single oral administration of 80 mg telmisartan (Reference 2) was 1600 ng·h/mL, and was comparable after co-administration with 75 mg clopidogrel (1570 ng·h/mL, Test 1) or clopidogrel given 30 min after intake of telmisartan (1560 ng·h/mL, Test 2). Thus, based on the evaluation of $AUC_{0-\infty}$, the relative bioavailability of telmisartan in the combination with clopidogrel relative to telmisartan alone was estimated to be 98%, or 97% if clopidogrel was given 30 minutes later. The 90% CI were always contained within the 80 - 125% limits.
The geometric mean C_{max} of telmisartan was 250 ng/mL after intake of telmisartan alone (Reference 2), decreased to 226 ng/mL with concomitant administration of clopidogrel (Test 1), but increased to 263 ng/mL when clopidogrel was given 30 min after intake of telmisartan (Test 2), which is a result of the high interindividual variability with regard to C_{max} (76.5 - 86.0 % gCV). Based on C_{max}, the point estimators were 90% and 104%, respectively.

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Efficacy results:
Pharmacokinetics:

Co-administration of telmisartan and clopidogrel had no influence on the pharmacokinetics of clopidogrel. Based on the evaluation of $AUC_{0-\infty,}$ the relative bioavailability of SR26334 in the combination of telmisartan with clopidogrel relative to SR26334 in clopidogrel alone was estimated to be 102%, or 101% if clopidogrel was given 30 minutes later. Based on $C_{max,}$ the point estimators were 91% respectively 99%. The 90% CI were always contained within the 80 - 125% limits.

A summary of the statistical evaluation of $AUC_{0-\infty}$ and C_{max} is given in the tables below:

Point estimators and 90% confidence intervals for analyte telmisartan

Comparison	Parameter	Lower Limit	Ratio [%] (T/R)	Upper Limit
T=Telm+Clop, R=Telmisartan	$AUC_{0-\infty}$	91.9	98.4	105.3
T=Telm+30minClop, R=Telm.	$AUC_{0-\infty}$	90.9	97.4	104.4
T=Telm+Clop, R=Telmisartan	C_{max}	77.5	90.4	105.4
T=Telm+30minClop, R=Telm.	C_{max}	88.7	103.6	121.1

Point estimators and 90% confidence intervals for analyte SR26334

Comparison	Parameter	Lower Limit	Ratio [%]	Upper Limit
T=Telm+Clop, R=Clopidogrel	$AUC_{0-\infty}$	98.3	102.0	105.9
T=Telm+30minClop, R=Clop.	$AUC_{0-\infty}$	96.8	100.5	104.4
T=Telm+Clop, R=Clopidogrel	C_{max}	83.9	91.0	98.7
T=Telm+30minClop, R=Clop.	C_{max}	90.9	98.7	107.2

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Safety results:	Eight subjects reported at least one adverse event, starting during screening in two cases, during washout after period 1 in three cases, during treatment with telmisartan in two cases, during treatment with telmisartan plus clopidogrel after 30 min. in one case and during clopidogrel in one case. All adverse events were of mild to moderate intensity. Headache was reported by three subjects. Back pain, toothache, dizziness, sciatica and increased heart rate were reported in one case each. Contact dermatitis was found in one case occurring within the wash-out phase after the first crossover period and led to treatment discontinuation for the second crossover period. A causal relationship between the event and the trial drug was assumed by the investigator in two cases of headache and in the case of dizziness, reported during treatment.
Conclusions:	Co-administration of telmisartan and clopidogrel and administration of clopidogrel 30 minutes after telmisartan had little impact on the pharmacokinetics of either telmisartan or SR26334. Telmisartan and clopidogrel were safe and well tolerated in the given single doses of 80 mg or 75 mg.