Boehringer Ingelheim

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 International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: MICARDIS®			
Name of active ingredient: Telmisartan		**Page: 1 of 4**	
Report date: 30 June 2003	**Trial- Number:** 502.327	**Study period (years):** 29 Oct 2001 to 31 Aug 2002	**Date of Revision:** XX September 2004

Title of study:	A Prospective, Randomized, Double-Blind, Forced Titration Trial to Compare the Efficacy of MICARDIS® (telmisartan 80 mg p.o. once daily) and Diovan® (valsartan 160 mg p.o. once daily) using Ambulatory Blood Pressure Monitoring (ABPM) in Patients with Mild to Moderate Hypertension After Missing One Dose
Investigator:	Multicenter study without official designation of a Principal or Coordinating Investigator
Study center(s):	Multicenter study without official designation of a Principal or Coordinating Investigator
Publication (reference):	N/A
Clinical phase:	IV
Objectives:	The primary objectives of the trial were to demonstrate that MICARDIS® (telmisartan) was statistically superior to Diovan® (valsartan) in the reduction of diastolic blood pressure (DBP) following a missed dose at the end of a 6 to 8 week treatment period as measured by the 24-hour ABPM mean and to demonstrate that MICARDIS® was statistically superior to Diovan® in the reduction of DBP during the last six hours of the 24-hour dosing interval as measured by ABPM following a dose of active study medication at the end of a 6 to 8-week treatment period.
Methodology:	Prospective, randomized, double-blind, double-dummy, parallel group, forced titration, comparison trial, using ABPM
No. of subjects:	
planned:	entered: 420
actual:	total enrolled: 490 MICARDIS®: 244 DIOVAN®: 246

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Diagnosis and main criteria for inclusion:	Patients age 18 years and older with mild-to-moderate hypertension defined as a mean seated DBP ≥95 mmHg and ≤109 mmHg and a 24-hour ABPM mean DBP ≥85 mmHg, each at baseline.
Test product:	MICARDIS® (telmisartan)
dose:	40 mg , once-daily, for two weeks, then forced titration to 80 mg, once-daily, for six weeks
mode of admin.:	Tablets, p.o.
batch no.:	
Duration of treatment:	8 weeks
Reference therapies:	1) DIOVAN® (valsartan) 2) Placebo
dose:	1) 80 mg, once-daily, for two weeks, then forced titration to 160 mg, once-daily, for six weeks 2) one tablet matching telmisartan 80 mg/one capsule matching valsartan 160 mg, once-daily
mode of admin.:	1) Capsules, p.o. 2) Tablet/capsule, p.o.
batch no.:	
Criteria for evaluation:	
Efficacy:	Change from baseline in the 24-hour ABPM mean DBP following a missed dose and change from baseline in the last 6-hour ABPM mean DBP of the 24-hour dosing interval following an active dose of study medication, both at the end of a 6 to 8-week treatment period.
Safety:	Adverse events, blood pressure and pulse rate monitoring.

Statistical methods: Analysis of covariance with treatment group and centre as main effects, and baseline as the covariate.

SUMMARY – CONCLUSIONS:

Efficacy results:

For the primary endpoint of the change from baseline in the last 6-hour ABPM mean DBP after an active dose of study medication, there was a significant (p=0.0136) difference between the adjusted mean changes for telmisartan (-7.6 mmHg) and valsartan (-5.8 mmHg). This adjusted mean difference of -1.8 mmHg (95% CI: -3.2 to -0.4 mmHg) in favor of telmisartan was supported by the fact that for each of the last six hours of the 24-hour dosing interval following an active dose, the reduction in the DBP hourly means was consistently greater for patients treated with telmisartan than for patients treated with valsartan.

For the primary endpoint of the change from baseline in the 24-hour ABPM mean DBP after a missed dose of study medication, there was no significant (p=0.0563) difference between the adjusted mean changes for telmisartan (-6.9 mmHg) and valsartan (-5.9 mmHg). When evaluating the 24-hour profiles of the hourly mean changes, this lack of significance appears to be due to the fact that the hourly mean changes for the two treatments were similar during the period from approximately 3 pm until 9 pm. However, from a secondary analysis a treat-by-centre interaction (p=0.0312), felt to be merely quantitative in nature was found. This led to the inclusion of the interaction term in the sensitivity analysis analyzing the per-protocol population. These results found the treatment-by-centre interaction not to be significant (p=0.2447) with a significant (p=0.0498, type II SS) adjusted mean treatment difference of -1.2 mmHg in favor of telmisartan.

The results regarding SBP are similar to those seen for DBP. The adjusted difference in the last 6-hour ABPM mean SBP after an active dose is -2.4 mmHg (p=0.0197) and in the 24-hour ABPM mean SBP is -1.6 mmHg (p=0.0945), both in favor of telmisartan 80 mg.

Analysis of secondary endpoints which reflect ABPM mean BP values during other time intervals after an active dose of study medication and after a missed dose, revealed that there is a consistent numerical advantage of telmisartan 80 mg over valsartan 160 mg which is greatest during the later hours of the dosing interval.

Analysis of secondary endpoints related to in-clinic mean BPs at trough, both after an active dose and after a missed dose, also revealed a consistent numerical advantage of telmisartan 80 mg over valsartan 160 mg.

Safety results:	Both treatments were well tolerated, with safety profiles similar to those of patients treated with placebo in previous studies. The overall incidence of adverse events was 38.1% and 30.9% for telmisartan and valsartan patients, respectively, the majority classified as mild or moderate in intensity. The most frequently reported adverse event was headache (telmisartan: 7.0%, valsartan: 5.3%). Other adverse events with an incidence of >2% in either treatment group were nasopharyngitis, dizziness, upper respiratory tract infection, and fatigue. Three patients (2 telmisartan and 1 valsartan) had a serious adverse event while on treatment and three (2 telmisartan and 1 valsartan) during the post-study period, none of which were considered related to study drug. No clinically significant change in pulse rate was observed throughout the study for either treatment group.
Conclusions:	Both treatments were effective and well tolerated in this patient population. This study replicates previous findings showing that once-daily dosing with telmisartan is effective at lowering blood pressure, and that its antihypertensive effects lasts throughout the entire 24-hour dosing interval, including the critical early morning period when the blood pressure surge occurs. Furthermore, this study demonstrated telmisartan to be statistically superior to valsartan at reducing both diastolic and systolic blood pressures during the last 6 hours of 24-hour dosing period following an active dose of medication. Additionally, telmisartan was found to be numerically more effective than valsartan in reducing the 24-hour mean DBP after a missed dose, even though the difference between treatments did not reach statistical significance.