Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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Name of company: Boehringer Ingelheim International GmbH		**Trial Synopsis**	Boehringer Ingelheim
Name of finished product: MICARDIS® HCT			
Name of active ingredients: Telmisartan and Hydrochlorothiazide		**Page: 1of 5**	
Report date: 15 December 2004	**Number:** 502.421	**Study period (dates):** 06 Sep 2003 - 14 Jun 2004	

Title of study:	A randomized, double-blind, double-dummy, placebo-controlled, forced-titration, comparison of MICARDIS® HCT (telmisartan 80 mg/ hydrochlorothiazide 25 mg) versus DIOVAN® HCT (valsartan 160 mg / hydrochlorothiazide 25 mg) using seated trough cuff blood pressure in patients with Stage 1 and Stage 2 hypertension.
Investigator:	Multicentre study without official designation of a Principal or Coordinating Investigator
Study centres:	109 sites
Publication (reference):	N/A
Clinical phase:	IV
Objectives:	The primary objective of this study was to show that MICARDIS® HCT (telmisartan 80 mg / hydrochlorothiazide 25 mg) is superior to placebo in lowering diastolic blood pressure (DBP) and systolic blood pressure (SBP), at least as effective DIOVAN® HCT (valsartan 160 mg / hydrochlorothiazide 25 mg) in lowering DBP, and possibly superior to DIOVAN® HCT in lowering DBP and SBP in patients with Stage 1 and Stage 2 hypertension as measured by seated trough cuff blood pressure monitoring.
Methodology:	Randomized, double-blinded, double-dummy, placebo-controlled forced-titration, parallel group comparison using seated trough cuff blood pressure.
No. of subjects:	
planned:	entered: 1035 patients
actual:	entered: 1109 patients Treatment A: MICARDIS®HCT (80/25) entered: 485 treated: 485 analysed (for primary endpoint): 467 Treatment B: DIOVAN®HCT (160/25) entered: 498 treated: 498 analysed (for primary endpoint): 479 Treatment C: Placebo entered: 126 treated: 126 analysed (for primary endpoint): 120
Diagnosis and main criteria for inclusion:	Male and Female patients ≥18 years of age with Stage 1 and Stage 2 hypertension defined as a baseline seated trough cuff DBP of ≥95 mmHg to <120 mmHg at Visit 2 (baseline)
Test product:	MICARDIS® (telmisartan 80 / HCTZ 25 mg)
dose:	80/25 mg (two 40/12.5 mg tablets)

mode of admin.:	Tablets p.o.
batch no.:	
Duration of treatment:	Eight weeks
Reference therapy:	DIOVAN® HCT (valsartan 160 / HCTZ 25 mg)
dose:	160/25 mg tablet
mode of admin.:	Oral tablets over-encapsulated
batch no.:	
Reference therapy:	Placebo
dose:	NA
mode of admin.:	Oral tablets (matching MICARDIS® HCT) and Oral tablets over-encapsulated (matching overencapsulated DIOVAN® HCT)
batch no.:	
Criteria for evaluation:	Primary endpoints:
	Change from baseline (Visit 2) for in-clinic seated trough cuff diastolic blood pressure (DBP) and systolic blood pressure (SBP) at the end of an eight week treatment period (Visit 6).
Efficacy:	Hierarchical Closed Testing Procedure:
	1) Superiority of MICARDIS®HCT 80/25 compared to placebo at the end of the eight week treatment period in the reduction of seated trough cuff DBP; if significant then,
	2) Superiority of MICARDIS®HCT 80/25 compared to placebo at the end of the eight week treatment period in the reduction of seated trough cuff SBP; if significant then,
	3) Non-inferiority of MICARDIS®HCT 80/25 compared to DIOVAN® HCT 160/25 at the end of the eight week treatment period in the reduction of seated trough cuff DBP; if significant then,
	4) Superiority of MICARDIS®HCT 80/25 compared to DIOVAN® HCT 160/25 at the end of the eight week treatment period in the reduction of seated trough cuff DBP; if significant then,
	5) Superiority of MICARDIS®HCT 80/25 compared to DIOVAN® HCT 160/25 at the end of the eight week treatment period in the reduction of seated trough cuff SBP.

	Secondary endpoints: Percentage of patients responding to treatment based on DBP and SBP mean trough cuff measurements. Percentage of patients who discontinue due to uncontrolled hypertension defined as SBP ≥180 mmHg and/or DBP ≥120 mmHg. ABPM sub-study: Descriptive data will be presented as a graphical representation of the by treatment hourly mean blood pressures over the 24-hour dosing interval at baseline and at the end of eight weeks treatment.
Safety:	Safety was evaluated by: - adverse events - measurement of changes from baseline in physical examinations, laboratory parameters and vital signs (mean SBP, mean DBP) and pulse rate.
Statistical methods:	Analysis of covariance with treatment as a main effect and baseline BP as a covariate; Mantel-Haenszel test controlling for centre.

SUMMARY – CONCLUSIONS:

Efficacy results:

For the primary endpoints of the change from baseline in the seated trough cuff DBP and SBP, telmisartan 80 / HCTZ 25 mg (T80/H25) was found to be superior to placebo (adjusted mean changes in seated trough cuff DBP and SBP of -17.6 and -24.0 mmHg, respectively, for T80/H25 compared to -6.8 and -4.4 mmHg, respectively, for placebo. As well, these changes from baseline for T80/H25 were statistically superior to those for valsartan 160 / HCTZ 25 mg (V160/H25) of -16.1 mmHg for DBP and -21.2 mmHg for SBP, with the adjusted mean differences being -1.5 mmHg for DBP (p=0.0096) and -2.8 mmHg for SBP (p=0.0026).

Secondary analysis on the primary endpoints of the changes from baseline in seated trough cuff DBP and SBP confirmed the overall significant treatment differences found in the primary analyses. No significant treatment-by-centre interaction was found when analyzing the changes from baseline in seated trough cuff SBP (p=0.5643). As well, when evaluating when evaluating only patients treated with either T80/H25 or V160/H25 no significant treatment-by-centre interaction was found in the changes from baseline in seated trough cuff DBP (p=0.1834). Further, the results of the analyses on the secondary endpoints of response rates for each of the four response criteria based on the seated trough cuff BPs found T80/H25 to have response rates that were significantly (p<0.0001) greater than placebo and that were consistently greater in magnitude than those for V160/H25.

Efficacy results cont:	From subgroup analyses on the primary endpoints, no significant treatment-by subgroup interactions for age group (<65 years old or ≥65 years old), gender, or race group (non-black or black) were found. For the subgroup of stage of hypertension at baseline there was some evidence of a treatment-by-stage interaction in the change from baseline in DBP (p=0.0120) and SBP (p=0.0608) which was not deemed to be qualitative in nature but rather largely influenced by differences between stage for the placebo treatment group which involved relatively few patients. The results of the ABPM sub-study found T80/H25 to be superior to placebo in the change from baseline for both DBP and SBP during each of the periods of the 24-hour dosing interval of last 6-hour mean, 24-hour mean, daytime, nighttime, and morning means. Due to the relatively small number of patients involved in the sub-study, no significant differences were found when comparing the effects on these ABPM endpoints of T80/H25 and V160/H25.

Safety results:	Overall, the trial confirmed the favorable safety profile for T80/H25 and V160/H25 compared to placebo The mean duration of treatment was comparable among the three treatment arms. No appreciable differences were noted in patients reporting one or more AEs in the T80/25 arm (207: 42.7%) and V160/H25 arm (188: 37.8%). A greater percentage of patients in the placebo arm (62: 49.2%) reported one or more AEs. The majority of the AEs in each treatment group were of mild or moderate intensity. Fourteen different AEs were reported by ≥2% of patients in at least one of the treatment arms. The most frequently reported AE during the randomized treatment period was headache (64 patients: 5.8%); 18 patients (3.7%) in the T80-T80/H25 arm, 31 patients (6.2%) in the V160-V160/H25 arm, and 15 patients (11.9%) in the placebo arm with the second most frequent AE being dizziness (39 patients: 3.5%); 22 patients (4.5%) in the T80-T80/H25 arm, 13 patients (2.6%) in the V160-V160/H25 arm, and 4 patients (3.2%) in the placebo arm. All other AEs were reported with an overall incidence of ≤2.5%. For AEs considered drug related by the Investigator, no appreciable differences were found between the monotherapies T80 with 18 patients (3.7%) and V160 with 23 patients (4.6%), or between the combination therapies of T80/H25 with 42 patients (9.0%) and V160/H25 with 35 patients (7.3%), or with 15 (11.9%) of the patients in the placebo arm reporting an AE considered drug related. Twenty-one patients reported SAEs during the trial: nine during the screening and/or run-in; ten during the randomization period; two post treatment. Of these patients, two were considered drug related (both in the T80-T80/H25 arm) and patients fully recovered. No patient deaths occurred during the study.
Conclusions:	• Both T80/H25 and V160/H25 were well tolerated and provided effective blood pressure control with acceptable safety profiles as compared to placebo. • T80/H25 produced statistically greater reductions in both seated trough cuff DBP and SBP compared to placebo and V160/H25. This study represents the first comparison of the two highest marketed strengths of MICARDIS® HCT and DIOVAN® HCT.