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		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: MICARDIS®				
Name of active ingredient: Telmisartan		**Page:** 1	**Number:**	
Ref. To Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: 3rd October 2003	**Number:** 502.317	**Study period (years):** 2000 -2002		

Title of study:	A PROBE (Prospective, Randomised, Open-Label, Blinded Endpoint) trial to investigate the efficacy and safety of Telmisartan 40-80mg once daily compared with 10-20 mg enalapril once daily over a period of 24 weeks in elderly patients with blood hypertension.
Investigator:	[redacted]
Study centre(s):	41 centres of hypertension (see attached list)
Publication (reference):	N/A
Clinical phase:	IV
Objectives:	**Primary objective**: to assess the efficacy of Telmisartan 40-80 mg once daily compared with enalapril 10-20 mg once daily in elderly patients with arterial hypertension in terms of change from baseline in 24-hour mean systolic blood pressure (SBP) at the end of the 8 weeks of monotherapy period of treatment (ABPM). **Secondary objectives**: to assess the efficacy of Telmisartan 40-80 mg once daily compared with enalapril 10-20 mg once daily in elderly patients with hypertension in terms of - SBP ABPM tracing profile at 8 and 24 weeks, analysed in blocks of 6 hours; - Changes from baseline in trough cuff (sphygmomanometer) SBP at 8 and 24 weeks; - Number of responders (sitting DBP< 90 mmHg and/or a fall of ≥ 10 mmHg; sitting SBP < 140 mmHg and/or a fall of ≥ 10 mmHg) at the end of monotherapy (8 weeks) and at the end of the study (24 weeks); - Number of controlled responders (sitting DBP < 90 mmHg and sitting SBP < 140 mmHg) at the end of monotherapy (8 weeks) and at the end of the study (24 weeks); - Smoothness index at 8 and 24 weeks; - Withdrawals due to lack of efficacy; to assess the tolerability of Telmisartan 40-80 mg once daily compared with enalapril 10-20 mg once daily in elderly patients with arterial hypertension in terms of - Incidence of adverse events; - Withdrawals due to adverse events.

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Report date: 3rd October 2003	**Number:** 502.317	**Study period (years):** 2000-2002		

Methodology:	Prospective, open-label, randomised, blinded endpoint, parallel group, clinical trial, with initial wash-out period				
No. Of subjects entered:					
Total:	Enrolled: 418		Randomised: 374		
Each treatment:	Telmisartan 192		enalapril 182		
Diagnosis and main criteria for inclusion:	Systolic hypertension in the elderly - Inclusion criteria 1. Age ≥ 65 years; 2. SBP ≥ 160 mmHg and any DBP (safety maximum of sitting DBP 110 mmHg), measured by manual cuff sphygmomanometer at the end of the wash-out period; 3. Written informed consent.				
Test product:	Telmisartan	and	Telmisartan	+	clonidine TTS1
Dose:	40 mg	and	80 mg	+	0.1 mg
Mode of admin.:	per os		per os		TTS
Batches no.:	902520 (40 mg tablets), 902475 (80 mg tablets), 942587 - 0017000A (clonidine)				
Duration of treatment:	2 weeks wash-out period, 24 weeks of treatment				
Test product:	enalapril	and	enalapril	+	clonidine TTS1
Dose:	10 mg	and	20 mg	+	0.1 mg
Mode of admin.:	per os		per os		TTS
Batches no.:	V244 – V434 – V522 – V559 – V569 – B319 (enalapril 5 mg); V518 – A1130 – A1442 (enalapril 20 mg); 942587 - 0017000A (clonidine				
Duration of treatment:	2 weeks wash-out period, 24 weeks of treatment				

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Criteria for evaluation:

Efficacy:

Primary: change from baseline in 24-hour mean SBP at the end of the 8 weeks of monotherapy period of treatment (ABPM).

Secondary: Changes from baseline in SBP at the end of the monotherapy period of treatment and at the end of the study, evaluated by sphygmomanometric blood pressure measurements and ABPM.-

Responder rate (sitting DBP < 90 mmHg and/or a fall of ≥ 10 mmHg; sitting SBP < 140 mmHg and/or a fall of ≥ 10 mmHg) at the end of monotherapy (8 weeks) and at the end of the study (24 weeks);

- Number of controlled responders (sitting DBP <90 mmHg and sitting SBP <140 mmHg) at the end of monotherapy (8 weeks) and at the end of the study (24 weeks);
- Smoothness index in comparison with baseline at 8 and 24 weeks;
- Withdrawals due to inadequate efficacy.

Safety:

Adverse events, DBP, HR, physical examination, routine laboratory tests

Statistical methods:

Efficacy: intent-to-treat and explanatory analysis for primary endpoint and intent-to-treat for secondary endpoints. Descriptive, analysis of variance/covariance, contingency tables, confidence intervals.

Safety: descriptive statistic tabulation by system organ class.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Primary end-point
There was no significant difference between the mean reduction in 24h SBP measured by ABPM in the two treatment groups after 8 weeks of monotherapy, both in the ITT and the PP patients populations:
-6.4 mmHg (95% CI –8.4, -4.4 mmHg) with Telmisartan versus –8.8 mmHg (95% CI –10.9, -6.7 mmHg) with enalapril (p=0.075) in the ITT population,
-6.7 mmHg (95% CI –8.8, -4.6 mmHg) with Telmisartan versus –8.9 mmHg (95% CI –11.0, -6.8 mmHg) with enalapril (p=0.10) in the PP population.
Secondary end-points
The ABPM analysis of 6h BP blocks, as well as the mean change in cuff SBP, responder rate, controlled responder rate and rate of withdrawals due to inefficacy consistently indicate that Telmisartan (40-80 mg) is as effective as enalapril (10-20 mg o. d.) both alone and in combination with clonidine TTS1 (1 patch weekly) in the treatment of systolic hypertension in the elderly.
The data also suggest that Telmisartan treatment may be associated with less variability in antihypertensive activity and therefore with a lower risk of episodes of excessive lowering of SBP than enalapril treatment.

Safety results:

Both study drugs were safe and well tolerated.
The overall incidence of adverse events was similar in the two treatment groups. 66 patients (34.4%) in the Telmisartan group reported 142 adverse events and 54 patients (29,7%) in the enalapril group reported 142 adverse event. A total of 18 adverse reactions were reported by 12 patients (6.2%) in the Telmisartan group; out of these 8 were reported during Telmisartan monotherapy by 6 patients. A total of 20 adverse reactions were reported by 13 patients (7.1%) in the enalapril group; out of these 10 were reported during enalapril monotherapy by 9 patients.
Six patients (3.1%) withdrew because of adverse events in the Telmisartan group and ten (5.5%) in the enalapril group.
Seven patients (3.6%) suffered 9 serious adverse events in the Telmisartan group and six patients (3.3%) suffered 9 serious adverse events in the enalapril group.
The most common adverse events were headache with both drugs, gastrointestinal disorders (mainly dyspepsia) with Telmisartan and cough with enalapril. In most cases they were related to study treatment and were therefore adverse reactions. Additional adverse reactions appeared when clonidine TTS1 was added: dry mouth and skin disorders (dermatitis and rash) in the Telmisartan group and hypotension (in one case associated with syncope) and skin disorders in the enalapril group. None of the adverse reactions were unexpected: headache is invariably reported with antihypertensive agents, cough is a well known adverse reaction to ACE inhibitors, dry mouth and skin disorders due to irritation at the site of application of the patch are common with clonidine TTS1.

Conclusions: In conclusion, Telmisartan (40-80 mg o. d.) is a safe and well tolerated antihypertensive agent, which is as effective as enalapril (10-20 mg o. d.) in the treatment of systolic hypertension in the elderly, given alone and in combination with clonidine TTS1. It may offer the advantage of a lower risk of nocturnal hypotensive episodes, which are a risk factor for cardiovascular events.