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:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** **to**		**Addendum No.:**
Report date: 17 September 2001	**Number:**	**Study period (years):** May 2000 – Febr 2001		

Title of study:	A Prospective, Randomised, Double-Blind, Double-Dummy, Titration-to-Response Trial Comparing MICARDIS® (telmisartan) (40 or 80 mg p.o. once daily) and COZAAR® / LORZAAR® (losartan) (50 or 100 mg p.o. once daily) in Patients with Mild-to-Moderate Hypertension using Ambulatory Blood Pressure Monitoring. (**TOPAS STUDY** = **T**elmisartan and **LO**sartan Com**P**arative **A**BPM **S**tudy).
Investigator:	[redacted]
Study centres:	37 centres in 11 countries in Europe, Canada, and South Africa
Publication (reference):	None at the time of this report.
Clinical phase:	IV
Objectives:	Primary objective: to demonstrate that MICARDIS® (telmisartan) is superior to COZAAR® / LORZAAR® (losartan) in lowering ambulatory diastolic blood pressure (DBP) during the last 6 hours of the 24-hour dosing interval as measured by ABPM after 8 weeks of treatment. Secondary objectives: 1) change from baseline in mean systolic blood pressure (SBP) during the last 6 hours of the 24-hour dosing interval as measured by ABPM, 2) changes from baseline in SBP and DBP during other periods during the 24-hour ABPM profile, 3) changes from baseline in mean seated trough SBP and DBP as measured by manual cuff sphygmomanometer, and 4) responder rates based on both ABPM and trough cuff blood pressure.
Methodology:	Prospective, randomised, double-blind, double-dummy, titration-to-response, parallel-group, comparison trial, using ABPM.
No. of subjects entered:	739 patients were enrolled and 352 patients discontinued prior to randomisation.
total:	387 patients were randomised
each treatment:	188 patients were randomised to telmisartan 40 mg, of whom 113 were titrated to the 80 mg dose; 199 patients were randomised to treatment with 50 mg losartan, of whom 135 were titrated to the 100 mg dose. A total of 367 patients completed the study.
Diagnosis and main criteria for inclusion:	Mild-to-moderate hypertension defined as: a mean seated DBP ≥95 mmHg and ≤109 mmHg, and 24-hour mean diastolic ABPM blood pressure ≥85 mmHg.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: MICARDIS®		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Telmisartan		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** **to**		**Addendum No.:**
Report date: 17 September 2001	**Number:**	**Study period (years):** May 2000 – Febr 2001		

Test product:	MICARDIS® (telmisartan).
dose:	40 - 80 mg, once daily.
mode of admin.:	Tablets for oral use.
batch no.:	902520 (40 mg), 902475 (80 mg), 001617 (placebo matching 40 mg), 9980237 (placebo matching 80 mg).
Duration of treatment:	8 weeks.
Reference therapy:	COZAAR® / LORZAAR® (losartan).
dose:	50 - 100 mg, once daily.
mode of admin.:	Tablets for oral use.
batch no.:	HK26620 (50 mg), B000102 (placebo matching 50 mg).
Criteria for evaluation:	
Efficacy:	**Primary**: Changes from baseline in DBP during the last 6 hours of the dosing interval as measured by ABPM. **Secondary**: Change from baseline in mean SBP during the last 6 hours of the 24-hour dosing interval as measured by ABPM; Changes from baseline in SBP and DBP during other periods during the 24-hour ABPM profile; Changes from baseline in mean seated trough SBP and DBP as measured by manual cuff sphygmomanometer; Responder rates based on both ABPM and trough cuff blood pressure. ABPM responder definitions: 1) DBP 'control' (24-hour mean DBP <80 mmHg). 2) DBP 'response' (24-hour mean DBP <80 mmHg or a reduction from baseline of ≥10 mmHg). 3) SBP 'response' (24-hour mean SBP <130 mmHg or a reduction from baseline of ≥10 mmHg). Trough cuff responder definitions: 1) DBP 'control' (DBP <90 mmHg). 2) DBP 'response' (DBP <90 mmHg and/or a fall of ≥10 mmHg). 3) SBP 'response' (SBP <140 and/or a fall of ≥10 mmHg). 4) Blood pressure 'high normal' (SBP <140 mmHg and DBP <90 mmHg).
Safety:	Evaluation of adverse events.

Name of company: Boehringer Ingelheim **Name of finished product:** MICARDIS®		**Tabulated Study Report** **SUPPLEMENTARY SHEET**		**(For National Authority Use only)**
Name of active ingredient: Telmisartan		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: 17 September 2001	**Number:**	**Study period (years):** May 2000 – Febr 2001		
Statistical methods:	Analysis of covariance; Cochran-Mantel-Haenszel test; tabulation of adverse events summarised by treatment group.			

SUMMARY - CONCLUSIONS:

Efficacy results:

Following a response based up-titration (if cuff DBP > 90 mmHg), and after a total of 8 weeks of treatment, the reduction of the last 6-hour mean DBP with telmisartan was 1.2 /1.5 mmHg greater than the mean reduction with losartan (-6.3 and -6.4 versus -5.1 and -4.9 mmHg, respectively for the intent-to-treat (ITT) and evaluable patient (EVAL) populations). The difference between the mean reduction was not statistically significant. The rates of up-titration after 4 weeks of treatment with low doses in the two groups were different: 62% of the telmisartan 40 mg (n=111) and 70% (n=134) of the losartan 50 mg treated patients.

Statistical evaluations of secondary ABPM endpoints including 24-hour, morning, daytime, night-time, and blood pressure (SBP and DBP) load, as well as trough cuff blood pressures also did not show significant differences between the effects of telmisartan and losartan in the reduction of DBP. The effects of the two treatments were similar for each of these periods during the 24-hour dosing interval.

The statistical findings the comparisons of the blood pressure changes from baseline were also confirmed by the blood pressure response variables after 8 weeks of treatment. The response rates for telmisartan were consistently higher compared to losartan, although statistically not significant.

No relevant difference between treatments was seen in ABPM heart rate or trough pulse rate.

Safety results:

Exposure was comparable among treatment groups. The median duration of exposure to active treatment was 57 days (28 days to the low dose, and 29 days to the high dose in each treatment group). The median exposure to placebo during the run-in phase was 29 days in both treatment groups.

Both treatments were well tolerated. The overall occurrence of adverse events was low. There were 42 patients (22.3%) who reported 66 adverse events with onset during treatment with 40 mg telmisartan, and 48 patients (24.1%) with 63 adverse events with onset during treatment with 50 mg losartan. Following titration to the higher doses, there were 25 patients (22.1%) who reported 37 adverse events with onset during treatment with 80 mg telmisartan, and 32 patients (23.7%) with 38 adverse events with onset during treatment with 100 mg losartan.

Headache was the most common adverse event with both active treatments (19 patients, 4.9%). Other frequently reported adverse events with onset during active treatment were increased blood pressure (13 patients, 3.4%), bronchitis (9 patients, 2.3%), upper respiratory tract infection (9 patients, 2.3%), and dizziness (8 patients, 2.1%). All other adverse events with an onset during active treatment were reported by less than 2% of the patients during treatment with losartan and telmisartan.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: MICARDIS®		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Telmisartan		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** **to**		**Addendum No.:**
Report date: 17 September 2001	**Number:**	**Study period (years):** May 2000 – Febr 2001		

Increased blood pressure was somewhat more often reported during treatment with losartan than with telmisartan. Dizziness and headache were more frequent during treatment with telmisartan. Otherwise, there were no relevant differences between treatments in the incidence of adverse events.

The intensity of the majority of all adverse events was mild. There were more mild adverse events with telmisartan than with losartan. The number and percentage of adverse events with moderate intensity was higher with losartan than with telmisartan. Ten patients had a severe adverse event with onset during active treatment, four of which were considered related to the trial medication. These adverse events were: fatigue (80 mg telmisartan), syncope (50 mg losartan), and impotence and increased blood pressure (both 100 mg losartan). All other severe adverse events were unrelated.

Overall, the majority of all adverse events was considered unrelated to the trial medication by the investigator. There were more patients with drug-related adverse events with losartan than with telmisartan.

In total 12 patients had a serious adverse event: one patient during the screening phase, six patients during the placebo run-in phase, and five patients during active treatment (n=2 on 40 mg telmisartan, n=1 on 80 mg telmisartan, and n=2 on 50 mg losartan). All serious adverse events were unrelated to treatment except one case of syncope with 50 mg losartan. For two patients, the event (myocardial infarction) had a fatal outcome (n=1 on 40 mg and 80 telmisartan each).

Nine patients prematurely discontinued from the trial due to adverse events: n=2 on 40 mg telmisartan, n=1 on 80 mg telmisartan, n=3 on 50 mg losartan and n=3 on 100 mg losartan. One patient had a temporary dose reduction. This patient took only one of the two double blind tablets on the first day of treatment with 50 mg losartan because the patient had mild abdominal pain.

Conclusions:

The reduction in DBP was larger after treatment with 40/80 mg telmisartan than after treatment with losartan 50/100 mg, but the difference of –1.2 mmHg in mean adjusted DBP reduction was statistically not significant.

Overall, both treatments were well tolerated. Telmisartan had a slightly better safety profile than losartan in this trial.

A pooled analysis with data from a similar study conducted in USA will be performed.