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: -				
Name of active ingredient: Crobenetine, BIII 890 CL		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 31 March 2003	**Number:** 599.12	**Study period (years):** February to April 2002		

Title of study:	Pharmacokinetics of 7.5 mg midazolam, given orally with and without concomitant administration of 175 mg crobenetine, given as a 6 hrs i.v. infusion (one hour loading dose directly followed by a five hours maintenance dose). A randomised, single blind, two-way crossover trial in healthy male subjects.
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Boehringer Ingelheim Pharma KG, Ingelheim, Germany
Publication (reference):	No
Clinical phase:	I
Objectives:	To assess the pharmacokinetics of midazolam with/without concomitant administration of crobenetine
Methodology:	Balanced, two-sequence, two-period, single-centre, open-label for midazolam, single blind for crobenetine, randomised, two-way crossover design
No. of subjects entered:	
total:	20 (19 completed)
each treatment:	20 (19 completed)
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 21 – 50 years, Bodymass index: 18.5 – 29.9 kg/m^2
Test product:	Midazolam tablet with crobenetine infusion
dose:	7.5 mg midazolam (tablet) and 175 mg/6 h crobenetine (5% mannitol solution)
mode of admin.:	Midazolam: Oral administration with 180 mL water. Crobenetine: 6 hrs two-step i.v. infusion (one hour loading dose + five hours maintenance dose).
batch no.:	Midazolam: B152001 BIII 890 CL: B000704
Duration of treatment:	Single p.o. dose of midazolam, 6 hours (i.v. infusion) for crobenetine
Reference therapy:	Midazolam and placebo
dose:	7.5 mg midazolam (tablet) and 175 mg/6 h Placebo (5% mannitol solution)

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mode of admin.:	Midazolam: Oral administration with 180 mL water. Placebo: 6 hrs two-step i.v. infusion (one hour loading dose + five hours maintenance dose.
batch no.:	Midazolam: B152001 Placebo: B000802
Criteria for evaluation:	
Efficacy:	***Pharmacokinetics:*** *primary endpoints:* C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$ of midazolam *secondary endpoints:* individual time courses of the drug plasma concentrations, and pharmacokinetic parameters of midazolam, 1-hydroxymidazolam and crobenetine
Safety:	Physical examination, vital signs (BP, PR), 12-lead ECG, clinical laboratory tests, adverse events and the evaluation of tolerability
Statistical methods:	Two-sided 95% CIs for expected median intra-subject (intra-individual) ratios of $AUC_{0-\infty}$, AUC_{0-tz} and C_{max} for midazolam and crobenetine were calculated. The statistical model was ANOVA on log transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". CIs are based on the residual error from ANOVA. Additionally, the corresponding point estimates for $AUC_{0-\infty}$, AUC_{0-tz} and C_{max} are provided. Descriptive statistics for all other parameters.

SUMMARY - CONCLUSIONS:

Efficacy results:

Pharmacokinetics:

No inhibition of midazolam metabolism upon co-administration of crobenetine was seen (95% confidence interval from 86.8 to 107.6% for C_{max} with a point estimate of 96.7%, from 89.5 to 107.8% for $AUC_{0-\infty}$ with a point estimate of 98.2%, and from 89.0 to 106.9% for AUC_{0-tz} with a point estimate of 97.6%).

There was some evidence that crobenetine influences the pharmacokinetics of the metabolism of midazolam metabolite (1-hydroxymidazolam) (95% confidence interval from 101.7 to 137.2% for C_{max} with a point estimate of 118.2%, from 99.9 to 130.6% for $AUC_{0-\infty}$ with a point estimate of 114.2%, and from 102.8 to 128.6% for AUC_{0-tz} with a point estimate of 115.0%). However, this effect is below the level (50%) predetermined to be clinically relevant.

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Safety results:

In general, there was no meaningful difference between treatment A (midazolam + crobenetine) and treatment B (midazolam + placebo). The most common adverse event reported by all subjects in both groups was severe fatigue which was classified as related to study treatment. This did not result in any treatment discontinuations. There were no meaningful changes in laboratory parameters, vital sign findings, or ECG findings. The global clinical assessment of tolerability was rated as good for all subjects. Only one site injection reaction was reported. One subject ([redacted]) sustained a concussion and laceration by accident during wash-out. This subject was therefore withdrawn prior to his second treatment. Overall, it is concluded that crobenetine was safe and well-tolerated in this trial.

Conclusions:

Crobenetine co-administration has been shown to have no clinically relevant impact on single dose midazolam pharmacokinetics, as evidenced by plasma midazolam concentrations and those of its active metabolite, 1-hydroxymidazolam.

There were no meaningful observations for the other safety parameters evaluated. Based on the observations of this trial, crobenetine is safe and well tolerated.