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: Not available				
Name of active ingredient: Epinastine + Pseudoephedrine		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: 10 May 2001	**Number:** **U01-3150**	**Study period (years):** 10 August 1999 to 14 October 1999		

Title of study:	Study of the pharmacokinetic interactions and relative bioavailability of epinastine and pseudoephedrine in healthy volunteers, comparing tablets containing the fixed combination of the two substances with tablets containing each of the two substances separately
Investigator:	[redacted]
Study centre(s):	[redacted]
Publication (reference):	R01-0293 (45)
Clinical phase:	I
Objectives:	To compare the bioavailable fraction of epinastine and pseudoephedrine when administered as a fixed combination in tablet form (new pharmaceutical formulation), with that obtained with each of these drugs when administered separately to healthy volunteers.
Methodology:	Comparative, open, randomised, cross over study using a Latin squares design in healthy volunteers, with an intermediate wash-out period of not less than one week.
No. of subjects entered:	25 healthy volunteers
total:	25
each treatment:	25
Diagnosis and main criteria for inclusion:	Healthy volunteers, aged between 21 and 45 years, with the written informed consent of the volunteer
Test product:	Epinastine plus Pseudoephedrine slow-release (SR) tablet (fixed combination)
dose:	10 mg plus 120 mg, respectively
mode of admin.:	Oral
batch no.:	F4861
Duration of treatment:	One single dose of each formulation. Observation period: 24 h.

Reference therapy:	Epinastine HCl tablet	Pseudoephedrine Sulfate tablet
dose:	10 mg	120 mg
mode of admin.:	Oral	Oral
batch no.:	F4859	F4860

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Not available				
Name of active ingredient: Epinastine + Pseudoephedrine		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: 10 May 2001	**Number:** **U01-3150**	**Study period (years):** 10 August 1999 to 14 October 1999		

Criteria for evaluation:

Efficacy:	Area under the curve (AUC), peak plasma concentration (Cp_{max}), time required to reach peak value (T_{max}), half-life ($T_{1/2}$) and Cp_{max}/AUC ratio.
Safety:	Physical examination, vital signs, recording of adverse events and withdrawals due to safety reasons.
Statistical methods:	The statistical method employed in this study primarily involved analysis of variance (ANOVA) for a two-way cross over study with three sources of variation: subjects, treatments and periods. Each variance was analysed using the F test at the 5% level of significance. Once the measurements of the drugs in the plasma samples were performed, the mean results with their descriptive statistics, individual values, with calculations of the pharmacokinetic parameters were obtained using the PKCAL program in their appropriate tables. The volunteers who did not, for whatever reason, adequately comply with the three periods of the study were replaced.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Not available				
Name of active ingredient: Epinastine + Pseudoephedrine		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: 10 May 2001	**Number:** **U01-3150**	**Study period (years):** 10 August 1999 to 14 October 1999		

SUMMARY - CONCLUSIONS:

Efficacy results:

Twenty-three volunteers were included in the pharmacokinetic analysis. The volunteer [redacted] did not receive the Epinastine plus Pseudoephedrine tablet and she was excluded of kinetic analysis.

The differences between mean values of T_{max}, Cp_{max}, AUC_t, AUC_∞ and Cp_{max} /AUC_t for both Epinastine and for Pseudoephedrine formulations were not significant.

The MKMODEL program showed that the Cp_{max}, AUC_t, AUC_∞ and Cp_{max} /AUC_t had a 90% confidence interval within the bioequivalence interval 0.80-1.25 from which it can be concluded, taking into account Schuirmann's test, as well as that of Hauck and Anderson, that the combination and single-agent formulations can be regarded as bioequivalent, both in terms of the bioavailable fraction and rate of absorption by the body.

With respect to the T_{max}, and based on the non-parametric confidence interval, it may not be concluded that the two Epinastine preparations are bioequivalent though bioequivalence may be shown for the two Pseudoephedrine preparations.

Analysis of the relative bioavailability of the combination formulation compared with the single-agent formulation showed that Cp_{max} and AUC_t in the case of Epinastine and Cp_{max}, AUC_∞ and AUC_t in the case of Pseudoephedrine the ratio was about 1.

The intervals calculated using the different methods were very similar, allowing outliers to be excluded.

None of the pharmacokinetic parameters of Epinastine and Pseudoephedrine studied showed any significant differences between the combined preparation and single-agent therapy. The 90% confidence intervals also suggested that there was no pharmacokinetic interaction between Epinastine and Pseudoephedrine in this combined preparation. As consequence, the results of the kinetic data analysis for these three treatments might support the bioequivalence hypothesis.

Safety results:

Twenty-five (25) healthy volunteers were included in the safety analysis. Two volunteers reported adverse events. One healthy volunteer reported blurred vision and headache and another one headache (volunteers [redacted] and [redacted], respectively). These adverse events were mild (blurred vision, volunteer [redacted], and headache in the case of volunteer [redacted]) and moderate (headache, volunteer [redacted]) and considered by the investigator as not related to trial medication. No concomitant medication was needed.

There were not Serious Adverse Events or other significant adverse events during the trial. No volunteer died during the study and no volunteer discontinued due to adverse events. There was not any significant laboratory abnormal result for those 25 volunteers included in the trial. Twelve volunteers showed some laboratory measurements out of normal range, however, in all cases the investigator considered them as not clinically significant.

Conclusions:

On the basis of the kinetic data, the combination formulation can be considered as bioequivalent to the single-agent formulations in the case of both Epinastine and Pseudoephedrine. The low incidence of adverse events with both single-agent formulation and the combination tablet indicates that the Epinastine and Pseudoephedrine formulations are safe.