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***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Mucosolvan®				
Name of active ingredient: Ambroxol		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 12 OCT 05	**Number:** U05-2210	**Study period (dates):** 23 SEP 04 - 03 FEB 05		

Title of study:	Relative bioavailability of ambroxol hydrochloride following oral administration of soft pastilles 15 mg (Test) compared to 15 mg of syrup (15mg/5mL) (Reference I) and compared to 15 mg of syrup (30mg/5mL) (Reference II) in healthy male and female volunteers. An open-label, randomised, single-dose, 3-way crossover study
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
Publication (reference):	Data of this study has not been published
Clinical phase:	I
Objectives:	To investigate the relative bioavailability of ambroxol hydrochloride soft pastilles 15 mg vs. ambroxol HCL 15 mg of syrup (15mg/5mL, Reference I) and ambroxol hydrochloride 15 mg of syrup (30mg/5mL, Reference II) in a fasted state
Methodology:	Open-label, randomised, single dose, three-way crossover design, period balanced
No. of subjects:	
planned:	24
actual:	24
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age ≥18 and ≤55 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	Ambroxol hydrochloride soft pastilles (T)
dose:	15 mg
mode of admin.:	Oral administration (for sucking) after an overnight fast with 240 mL water
batch no.:	4001
Duration of treatment:	One day (single dose p.o.) for each treatment
Reference therapy:	Ambroxol hydrochloride syrup (15mg/5mL) (R I) Ambroxol hydrochloride syrup (30mg/5mL) (R II)
dose:	15 mg (5 mL RI, 2.5 mL, RII)

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mode of admin.:	p.o. administration after an overnight fast with 240 mL water
batch no.:	415599 and 415596
Criteria for evaluation:	
Efficacy:	Pharmacokinetics primary endpoints: $AUC_{0-\infty}$ and C_{max} secondary endpoints: individual time courses of the drug plasma concentrations, AUC_{0-tz}, t_{max}, $t_{1/2}$, MRT_{po}, CL/F, V_z/F
Safety:	Physical examination, BP, PR, ECG, laboratory tests, adverse events and tolerability
Statistical methods:	Point estimators (geometric means) of the median intra-subject ratios of $AUC_{0-\infty}$ and C_{max} and their two-sided 90% and 95% CIs were calculated. The statistical model was ANOVA on log transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". CIs were based on the residual error from ANOVA. Descriptive statistics for all other parameters were calculated.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetics:

Pharmacokinetic results were derived from plasma concentration-time data of ambroxol hydrochloride after single oral administration of 15 mg ambroxol hydrochloride given as soft pastille and as two different syrup formulations.

The maximum plasma concentration was reached after 1.49 hours (median) for the soft pastille (test treatment), after 1.50 hours (median) for reference I (5 mL of a 15 mg/5 mL syrup) and after 1.49 hours (median) for reference II (2.5 mL of a 30 mg/5 mL syrup).

Geometric mean values of C_{max} (%gCV) were 24.8 ng/mL (30.9%) for the soft pastille, 22.6 ng/mL (20.3%) for reference I and 23.4 ng/mL (21.4%) for reference II. The 90% confidence interval for maximum plasma concentration ranged from 102% to 117% with a point estimate of 109% for the comparison soft pastille versus reference I. For the comparison soft pastille versus reference II, the confidence interval for C_{max} ranged from 98.7% to 114% with a point estimate of 106%.

Geometric mean values of $AUC_{0-\infty}$ (%gCV) were 222 ng·h/mL (33.2%) for the soft pastille, 201 ng·h/mL (25.7%) for reference I and 204 ng·h/mL (26.0%) for reference II. The 90% confidence interval for $AUC_{0-\infty}$ ranged from 104% to 118% with a point estimate of 111% for the comparison soft pastille versus reference I. For the comparison soft pastille versus reference II, the confidence interval for $AUC_{0-\infty}$ ranged from 102% to 116% with a point estimate of 109%.

Secondary pharmacokinetic parameters do not show significant differences between the test and the two reference formulations.

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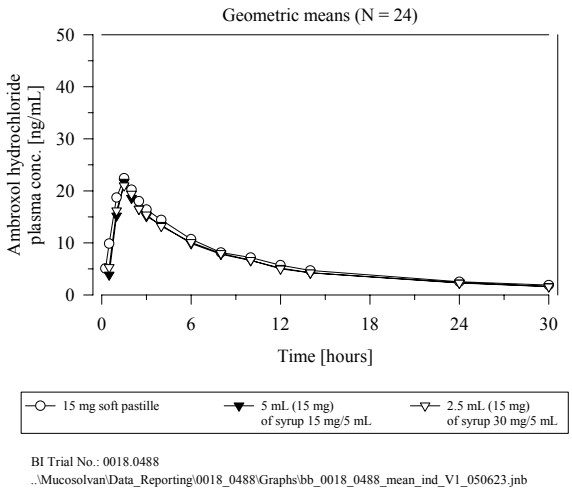

Figure 2.1: Geometric mean drug plasma concentration-time profiles of Ambroxol HCl after oral administration of 15 mg Ambroxol HCL given as soft pastille, as 5 mL of a 15 mg/5 mL syrup and as 2.5 mL of a 30 mg/5 mL syrup

Safety results: Nasopharyngitis of mild intensity was the only adverse event reported by one subject. No causal relationship between the event and the trial drug was assumed by the investigator.

Conclusions: Relative bioavailability of ambroxol hydrochloride for the soft pastille formulation compared to the two syrup formulations amounts to approximately 109%. Bioequivalence was shown for the soft pastille formulation in comparison to the two syrup formulations.

Ambroxol was safe and well tolerated in the given single dose of 15 mg.