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: Mucosolvan				
Name of active ingredient: Ambroxol hydrochloride		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: January 17, 2000	**Number:** 18.479	**Study period (years):** 1999		

Title of study:	An open label, randomised, two-way crossover study in healthy female and male volunteers to evaluate the relative bioavailability of a 20 mg ambroxol hydrochloride lozenge in comparison to 30 mg ambroxol hydrochloride syrup (Mucosolvan®).
Investigator:	[redacted]
Study center:	Human Pharmacology Centre, Biberach / Riss, Germany
Publication (reference):	N.A.
Clinical phase:	I
Objectives:	To investigate the relative bioavailability of a 20 mg ambroxol hydrochloride lozenge compared to 30 mg ambroxol hydrochloride syrup (Mucosolvan®) after dose normalisation.
Methodology:	Single dose, randomised, open label, period balanced crossover trial.
No. of subjects entered:	
total:	20 (10 female / 10 male)
each treatment:	20 (10 female / 10 male)
Diagnosis and main criteria for inclusion:	healthy female and male volunteers of 18-55 years old, with a Broca Index of > -20 % and < + 20 %
Test product:	Ambroxol hydrochloride lozenge
dose:	20 mg
mode of admin.:	Per oral
batch no.:	802 234
Duration of treatment:	single dose
Reference therapy:	Ambroxol hydrochloride syrup (Mucosolvan®)
dose:	30 mg
mode of admin.:	Per oral
batch no.:	810247
Criteria for evaluation:	
Efficacy/ Pharmacokinetics:	Individual and average C_{max}, $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, λ_z, AUC_{0-t}, MRT_{tot}, CL/f and V_z/f
Safety:	Blood pressure, pulse rate, ECG, adverse events and laboratory tests

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Statistical methods: Descriptive statistical analysis and 95% confidence intervals for pharmacokinetic parameters

SUMMARY - CONCLUSIONS:

Efficacy results: n.a.

Pharmacokinetic results:

Ambroxol in plasma was measured by an HPLC assay with ultraviolet detection. The limit of quantification was 1.0 ng/mL. Quality controls with an assay precision within ±3.4 % and a deviation from theory within ±1.7 % demonstrated adequate assay performance.

Twenty subjects were enrolled and eighteen subjects were evaluable for pharmacokinetic analysis. Volunteers participating in that trial had a mean age of 33.9 years (range: 19 to 48 years), a mean weight of 70.3 kg (range: 54.0 to 84.0 kg) and a mean height of 173.7 cm (range: 160 to 187 cm).

The C_{max} was reached after app. 1.75 hours (median) for the syrup [R = reference] and after app. 2.50 hours (median) for the lozenge [T = test] formulation.

Geometric mean values C_{max} (%gCV) were 31.6 ng/mL (32.7 %) [T] vs. 38.5 ng/mL (37.0 %) [R] and normalised (per mg) geometric mean values amounted 1.58 ng/mL (32.7 %) for the lozenge vs. 1.28 ng/mL (37.0 %) for the syrup. The 95 % confidence interval for dose adjusted C_{max} ranged from 108 % to 141 % with a point estimate of 123 %.

True geometric mean $AUC_{0-\infty}$ values (%gCV) were 339 ng·h/mL (29.0 %) [T] vs. 408 ng·h/mL (39.7 %) [R] and normalised (per mg) geometric mean values amounted 17.0 ng·h/mL (28.9 %) for the lozenge vs. 13.6 ng·h/mL (39.7 %) for the syrup. The 95 % confidence interval for dose adjusted $AUC_{0-\infty}$ ranged from 116 % to 134 % with a point estimate of 125 %.

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TABLE 2.1: Results of the noncompartmental pharmacokinetic evaluation (N=18). Source data in TABLE 14.4.1 to 14.4.3

		syrup 30 mg		lozenge 20 mg			
		gmean	gCV [%]	gmean	gCV [%]		
C_{max}	[ng/mL]	38.5	37.0	31.6	32.7		
t_{max}	[h]	1.75#	0.75-3.00§	2.50#	1.50-3.00§		
$AUC_{0-\infty}$	[ng·h/mL]	408	39.7	339	29.0		
AUC_{0-t}	[ng·h/mL]	363	39.2	304	28.6		
$AUC_{t-\infty}$	[%]	9.76	50.9	9.56	41.4		
λz	[1/h]	0.0680	23.0	0.0679	30.6		
$t_{½}$	[h]	10.2	23.1	10.2	30.6		
MRT_{tot}	[h]	9.77	16.1	9.57	16.3		
CL/f	[mL/min]	1230	39.7	985	29.1		
Vz/f	[L]	1080	31.2	869	36.2		
normalised per mg		gmean	gCV [%]	gmean	gCV [%]	point estimate [%]	95% CI [%]
NC_{max}	[ng/mL]	1.28	37.0	1.58	32.7	123	108 - 141
$NAUC_{0-\infty}$	[ng·h/mL]	13.6	39.7	17.0	28.9	125	116 - 134

median; § range

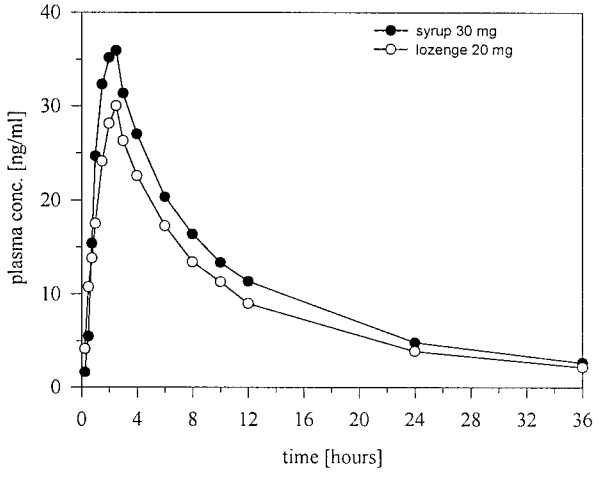

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FIGURE 2.1: Geometric mean plasma concentration of ambroxol after application of either 20 mg ambroxol hydrochloride given as lozenge or 30 mg ambroxol hydrochloride given as syrup in healthy volunteers (N=18). Source Data in TABLES 1 and 2 of APPENDIX 16.3.2.1

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Safety results:

Ambroxol hydrochloride lozenge as well as Ambroxol hydrochloride syrup was safe and well tolerated in this trial. Four of 20 subjects reported a total of 5 adverse events (two events of diarrhoea, one event of headache, dermatitis and tooth ache). These events were not considered to be drug related and were mild to moderate in intensity. There were no serious adverse events. There were no clinically relevant changes in vital signs, EKG, laboratory values and physical examination.

Conclusions:

Both ambroxol formulations (lozenge and syrup) were well tolerated in this trial by healthy volunteers. Assay performance for determination of ambroxol in plasma was adequate. The relative bioavailability of the ambroxol lozenge formulation compared to a calculated equivalent dose of ambroxol syrup amounts approximately 125 %.