Clinical Study Synopsis for Public Disclosure

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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 Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-005114-52	
Name of active ingredient: Ambroxol		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 JUL 2009	**Trial No. / U No.:** 18.494 / U09-1711-01	**Dates of trial:** 28 OCT 2008 – 11 DEC 2008	**Date of revision** (if applicable)**:** Not applicable

Title of trial:	Investigation of the metabolism and pharmacokinetics of an open label single dose of 20 mg ambroxol administered as a lozenge together with an oral solution of 0.4 mg [^{14}C]-ambroxol in healthy male volunteers
Principal/Coordinating Investigator:	[redacted]
Trial sites:	[redacted] The Netherlands
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	To determine the basic pharmacokinetics of ambroxol and [^{14}C]-radioactivity including mass balance, excretion pathways and complete metabolism in healthy male volunteers following administration of a lozenge of 20 mg ambroxol together with an oral solution of 0.4 mg [^{14}C]-ambroxol labelled in two different positions
Methodology:	Open label absorption, distribution, metabolism and excretion (ADME) study with two groups of 6 male subjects receiving a lozenge of 20 mg ambroxol together with an oral solution of 0.4 mg [^{14}C]-ambroxol; each group received a different label
No. of subjects:	
planned:	entered: 12 (6 per group)
actual:	entered: 12 (6 per group) Treatment 0.4 mg [^{14}C]-cyclohexane ambroxol, (see test product 1, below) + 20 mg ambroxol in lozenge: entered: 6 treated: 6 analysed (for primary endpoint): 6 Treatment 0.4 mg [^{14}C]-benzyl ambroxol, (see test product 2, below) + 20 mg ambroxol in lozenge: entered: 6 treated: 6 analysed (for primary endpoint): 6
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥18 and ≤65 years, body mass index (BMI) range: ≥18.5 and ≤29.9 kg/m^2

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Test product 1:	Ambroxol HCl[cyclohexane-^{14}C(U)] (*Trans*-4(2-Amino-3,5-dibromo-benzylamino)-[^{14}C(U)]-cyclohexanol hydrochloride)
dose:	0.4 mg [^{14}C]-ambroxol containing approximately 1.85 MBq [^{14}C]-radioactivity in 1.0 mL
mode of admin.:	Oral solution
batch no.:	Not applicable
Test product 2:	Ambroxol HCl[benzyl-^{14}C] (*Trans*-4(2-Amino-3,5-dibromo-[^{14}C]-benzylamino)-cyclohexanol hydrochloride)
dose:	0.4 mg [^{14}C]-ambroxol containing approximately 1.85 MBq [^{14}C]-radioactivity in 1.0 mL
mode of admin.:	Oral solution
batch no.:	Not applicable
Test product 3:	Ambroxol HCl (*Trans*-4[(2-Amino-3,5-dibromo-benzylamino]-cyclohexanol hydrochloride; Mucoangin®, Boehringer Ingelheim, NL)
dose:	20 mg
mode of admin.:	Lozenge
batch no.:	719772
Reference therapy:	Not applicable
dose:	Not applicable
mode of admin.:	Not applicable
batch no.:	Not applicable
Duration of treatment:	One day (single-dose)

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Name of active ingredient: Ambroxol		**Page:** 3 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 JUL 2009	**Trial No. / U No.:** 18.494 / U09-1711-01	**Dates of trial:** 28 OCT 2008 – 11 DEC 2008	**Date of revision** (if applicable)**:** Not applicable

Criteria for evaluation:

Efficacy / clinical pharmacology: Pharmacokinetic (PK) parameters were assessed from the plasma and urinary concentrations of ambroxol, from the plasma and urinary concentrations of a major metabolite dibromoanthranilic acid (DBAA), and from the whole blood, plasma, urinary and faecal concentrations of [^{14}C]-radioactivity, using noncompartmental methods. Individual time course profiles of [^{14}C]-radioactivity in whole blood, plasma, urine and faeces, individual time course profiles of ambroxol in plasma and urine, rate and extent of excretion and mass balance based on the total radioactivity in urine and faeces, and the C_{blood}/C_{plasma} and $C_{blood\ cells}/C_{plasma}$ ratio of [^{14}C]-radioactivity were determined. In addition, metabolite structures and identification of major metabolites in plasma, urine, and faeces were to be elucidated and compared with various animal species. These results will be provided in a subsequent report.

Safety: Physical examination, vital signs (blood pressure and pulse rate), adverse events (AEs), tolerability, 12-lead electrocardiogram (ECG) and clinical laboratory tests

Statistical methods: Descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results: After administration to 12 subjects of a 20 mg ambroxol lozenge plus 0.4 mg [^{14}C]-ambroxol labelled in either the cyclohexane or benzyl ring, samples of blood, urine and faeces were collected and PK parameters were determined. Data were complete with the exception of urine PK measurements from one subject [redacted] who was noncompliant with urine collection.

The single dose plasma PK profiles for ambroxol were comparable between subjects receiving the [^{14}C]-cyclohexane and [^{14}C]-benzyl labels and were consistent with data from a previous study in which a 20 mg ambroxol lozenge was administered. The geometric mean half-life of ambroxol in plasma was 10.4 h. Ambroxol was detected in plasma for 48 h, and maximum concentrations of 31.8 to 113 nmol/L occurred between 0.75 to 3.0 h after study medication administration.

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Name of active ingredient: Ambroxol		**Page:** 4 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 JUL 2009	**Trial No. / U No.:** 18.494 / U09-1711-01	**Dates of trial:** 28 OCT 2008 – 11 DEC 2008	**Date of revision** (if applicable)**:** Not applicable

Efficacy / clinical pharmacology results: (continued)

Similar to ambroxol, the plasma PK profiles for a major metabolite dibromoanthranilic acid (DBAA) were consistent between subjects receiving the [^{14}C]-cyclohexane and [^{14}C]-benzyl labels, as expected. The metabolite DBAA was not detectable in plasma for the first hour after ambroxol administration, but then persisted for 96 hours, with maximal levels 3-4 fold higher than the parent drug (gMean values). DBAA concentrations peaked between 6 to 24 hours, ranging in values from 175 to 429 nmol/L. The geometric mean half-life of DBAA was 24 h (range 20.9 to 29.2 h), considerably longer than that of ambroxol.

For both [^{14}C]-labels, the half-lives of total radioactivity in blood and plasma were greater than 20 hours, demonstrating the persistence of metabolites with longer half-lives than ambroxol. For [^{14}C]-radioactivity in plasma, in contrast to ambroxol and DBAA, significant differences were apparent between the two radioactive labels in the PK parameters measured, with higher values of $AUC_{0-\infty}$ and C_{max} determined for [^{14}C]-benzyl radioactivity relative to [^{14}C]-cyclohexane radioactivity. These differences indicate that metabolite(s) containing the benzyl portion of the ambroxol molecule are accumulated at higher levels relative to those containing the cyclohexane portion. Similar differences were also seen for [^{14}C]-radioactivity in whole blood. For the [^{14}C]-cyclohexane group, ambroxol accounted for approximately 7% of the observed radioactivity, indicating that metabolites were responsible for the other 93%. For the [^{14}C]-benzyl group, ambroxol accounted for approximately 3% of the observed radioactivity and the metabolite DBAA around 55%, indicating that other metabolites accounted for a smaller proportion of the radioactivity (42%) in this case.

Considering both dose groups together, mass balance of 96.6 ± 1.6% of the actual radioactive dose administered was collected in urine (90.0 ± 1.9%) and faeces (6.5 ± 0.7%) over 144 hours (6 days), demonstrating that ambroxol and its metabolites are primarily eliminated in the urine. Unchanged ambroxol was present in urine at <5% of the administered dose, indicating extensive metabolism of the parent compound. The renal clearance of ambroxol was approximately 50 mL/minute. Less than 0.3% of the ambroxol dose administered was recovered in the urine as DBAA.

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Name of active ingredient: Ambroxol		**Page:** 5 of 6	**Synopsis No.:**
Module:		**Volume:**	
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Efficacy / clinical pharmacology results: (continued)	With regard to blood/plasma partitioning of radioactivity, the concentrations of radioactivity in a mL of blood were significantly less than in a mL of plasma. Comparing the geometric mean C_{max} values for blood and plasma, the ratios observed of 0.61 ([^{14}C]-cyclohexane) and 0.55 ([^{14}C]-benzyl) were roughly equivalent to the hematocrit (~0.45); thus, only minimal amounts of radioactivity partitioned into the erythrocyte fraction.
Safety results:	All 12 subjects completed the study as planned. No SAEs and no deaths occurred during the study. Over the course of the study, 6 subjects (50%) reported a total of 9 AEs. One subject (8%) reported one AE during screening, four subjects (33%) reported six AEs during administration of trial medication, and one subject (8%) reported two AEs during the post-treatment phase. All AEs reported during the study were classified as mild, and all events had resolved by the end of the observation period. Only one AE, a headache in [redacted] was considered by the investigator to be related to the study drug, and was treated with paracetamol. Paracetamol was also given for a post-treatment headache in [redacted]. No other concomitant therapies were required. Headache was the most commonly reported AE (3 of 9 events). No other AE was reported by more than one subject. No clinically relevant changes in laboratory parameters, vital signs, or ECGs were observed. Tolerability of ambroxol was assessed as 'good' for all subjects.

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Module:		**Volume:**	
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Conclusions:

After administration of a 20 mg ambroxol lozenge plus 0.4 mg [^{14}C]-ambroxol, the overall recovery of [^{14}C]-radioactivity was 97%. The major route of elimination of [^{14}C]-ambroxol radioactivity was found to be via urine (approximately 90%). However, <5% of the administered ambroxol dose was excreted in urine, and only 0.3% of ambroxol was excreted in urine as DBAA, indicating that other metabolites accounted for the vast majority of the urinary radioactivity. For ambroxol and for [^{14}C]-radioactivity, maximum plasma concentrations were reached around 2 hours after dosing, whereas for the major metabolite DBAA they were reached between 6 and 24 hours after dosing. The gMean terminal half-life ($t_{1/2}$) in plasma was 10.4 h for ambroxol, 24.2 h for DBAA and 26.5 h for [^{14}C]-radioactivity, indicating the presence of metabolites in plasma with longer terminal half-lives than ambroxol. Comparison between the two radioactive labels indicated a higher exposure to radioactivity administered in the [^{14}C]-benzyl group of ambroxol. For the [^{14}C]-cyclohexane group, ambroxol accounted for approximately 7% of the observed plasma radioactivity and other metabolites for 93%. For the [^{14}C]-benzyl group, ambroxol accounted for approximately 3% of the observed radioactivity, DBAA for 55%, and other metabolites for 42%. Comparison of radioactivity in whole blood and plasma demonstrated that only minimal amounts of ambroxol or its metabolites partitioned into the erythrocyte fraction.

Single doses of a 20 mg ambroxol lozenge along with 0.4 mg of [^{14}C]-ambroxol were safe and well tolerated in healthy male volunteers. The results of this study do not indicate any safety concerns for administration of ambroxol.