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: Bisoltussin® syrup Silomat® DMP soft pastilles		**EudraCT No.:** 2008-004532-20	**Synopsis No.:**
Name of active ingredient: Dextromethorphan hydrobromide monohydrate		**Page:** 1 of 7	
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Report date: 29 OCT 2009	**Trial No. / U No.:** 1134.2 / U09-2163-01	**Date of trial:** 20 JAN 2009 – 25 FEB 2009	**Date of revision:** Not applicable

Title of trial:	A phase I, single dose, controlled two-way crossover trial to evaluate the relative bioavailability of orally administered dextromethorphan syrup (21 mg dextromethorphan hydrobromide monohydrate) in comparison to dextromethorphan soft pastilles (21 mg dextromethorphan hydrobromide monohydrate) in healthy male and female subjects who are extensive metabolisers for cytochrome P450 (CYP) 2D6
Principal Investigator:	[redacted]
Trial site:	[redacted], Germany
Publication (reference):	Data of this trial has not been published.
Clinical phase:	I
Objectives:	To investigate the relative bioavailability of orally administered dextromethorphan syrup in comparison to dextromethorphan soft pastilles in healthy male and female subjects who are extensive metabolisers of CYP 2D6
Methodology:	Open-label, randomised, two way crossover
No. of subjects:	
planned:	entered: 18
actual:	entered: 18 Treatment dextromethorphan syrup (test): treated: 18 analysed (for primary endpoint): 18 Treatment dextromethorphan pastilles (reference): treated: 18 analysed (for primary endpoint): 18
Diagnosis and main criteria for inclusion:	Healthy male and female subjects, age ≥18 and≤55 years, body mass index range ≥18.5 and ≤30 kg/m^2, extensive metabolisers of CYP 2D6

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Test product:	Dextromethorphan syrup (Bisoltussin® Syrup)
dose:	21 mg dextromethorphan hydrobromide monohydrate (10.5 mL syrup)
mode of admin.:	Oral
batch no.:	PR08/10384 (Bulk 718946)
Reference therapy:	Dextromethorphan soft pastilles (Silomat® DMP soft pastilles)
dose:	21 mg dextromethorphan hydrobromide monohydrate (2 pastilles)
mode of admin.:	Oral
batch no.:	PR08/10384 (Bulk 20089908)
Duration of treatment:	Single doses of the treatments were administered on Day 1 of each period. There was a washout period of at least 7 days between treatments.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Pharmacokinetic parameters for dextrorphan (total and free; total = conjugated plus free) and dextromethorphan, 3-hydroxy-morphinan (total and free) and 3-methoxy-morphinan: Primary endpoints: $AUC_{0-\infty}$, C_{max}, and t_{max} for dextromethorphan and dextrorphan (total and free) Secondary endpoints: AUC_{0-tz}, AUC_{t1-t2}, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2,}$ MRT_{po}, CL/F, V_z/F, for all analytes (if feasible), $AUC_{0-\infty}$, C_{max}, and t_{max} for 3-hydroxy-morphinan (total and free) and 3-methoxy-morphinan
Safety:	Physical examination, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (including QT interval and heart rate corrected QTcF and QTcB), clinical laboratory tests, adverse events and tolerability

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Statistical methods:

Descriptive statistics for pharmacokinetic endpoints were calculated.

For the primary endpoints $AUC_{0-\infty}$ and C_{max}, an analysis of variance with the effects 'treatment', 'period', 'sequence', and 'subjects within sequences' was performed after logarithmic data transformation. Point estimators for the test/reference ratio and 90% confidence intervals were calculated.

A non-parametric analysis of t_{max} was done.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Dextromethorphan

Maximum exposure, represented by geometric mean C_{max}-values, is lower for the Test compared with the Reference product (0.887 ng/mL and 1.22 ng/mL, respectively). Ranges of observed C_{max}-values (minimum to maximum) are broad and similar for both products with 0.269 ng/mL to 8.39 ng/mL for Test and 0.329 ng/mL to 10.5 ng/mL for Reference.

Total exposure (extent of bioavailability), represented by geometric mean AUC_{0-tz}- or $AUC_{0-\infty}$-values, is lower for the Test compared with the Reference product with 5.14 h*ng/mL and 7.73 h*ng/mL for AUC_{0-tz} or 9.26 h*ng/mL and 12.4 h*ng/mL for $AUC_{0-\infty}$, respectively).

Mean dextromethorphan plasma profiles as well as AUC_{0-tz}- and C_{max}-values determined as primary pharmacokinetic characteristics after administration of Test and Reference suggest a slightly higher bioavailability of the soft pastilles compared to the syrup. However, considering the problems to determine parent compound with sufficient sensitivity and precision (even with an advanced analytical procedure – which was appropriately validated as indicated by QC results - compared to earlier studies), this conclusion remains preliminary.

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Efficacy / clinical pharmacology results, cont.:

As expected, differences already derived from the plasma concentration vs. time profiles as well as from the pharmacokinetic parameters were confirmed by the statistical evaluation. Parametric point estimate of 78.9 % was calculated for $AUC_{0-\infty}$ comparing Test vs. Reference with an affiliating confidence interval of 69.9 – 89.1 %. Point estimate for C_{max} was calculated as 75.9 % with an affiliating confidence interval of 67.0 – 85.9 %. Thus, the observed trend to lower values after administration of the syrup formulation was verified by this statistical estimation.

Dextrorphan (unconjugated)

Mean plasma concentration vs. time curves of unconjugated dextrorphan as well as the primary parameters $AUC_{0-\infty}$ and C_{max} indicate similar total and only slightly different maximum exposure after administration of Test and Reference.

Maximum exposure, represented by geometric mean C_{max}-values is only slightly lower for the Test compared with the Reference product (1.93 ng/mL and 2.17 ng/mL, respectively). Ranges observed for C_{max}-values (minimum to maximum) are broad but similar for both products with 0.639 ng/mL to 5.49 ng/mL for Test and 0.410 ng/mL to 4.89 ng/mL for Reference.

Total exposure (extent of bioavailability), represented by geometric mean AUC_{0-tz}- or $AUC_{0-\infty}$-values, is similar for Test and Reference with 10.0 h*ng/mL and 10.5 h*ng/mL for AUC_{0-tz} or 12.0 h*ng/mL and 12.8 h*ng/mL for $AUC_{0-\infty}$, respectively.

Findings already derived from plasma concentration vs. time profiles and pharmacokinetic parameters are principally confirmed by the results from the statistical evaluation. While bioequivalence was assessed for total exposure of both investigational products the lower limit of BE acceptance criteria was deceeded for maximum exposure. This however, is primarily due to the very high variability of more than 30 % observed for C_{max}-values. On the other hand, absorption occurs more rapidly after administration of Reference compared to Test.

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Efficacy / clinical pharmacology results, cont.:

Total (free and conjugated) dextrorphan

Descriptive statistics of the maximum exposure, represented by geometric mean C_{max}-values are almost identical for Test and Reference product (272 ng/mL and 278 ng/mL, respectively).

Extent of bioavailability, represented by geometric mean AUC_{0-tz}- and $AUC_{0-\infty}$-values, is also very similar for Test or Reference with 1370 h*ng/mL or 1350 h*ng/mL for AUC_{0-tz} and 1380 h*ng/mL or 1370 h*ng/mL for $AUC_{0-\infty}$, respectively.

Mean plasma concentration vs. time curves of total dextrorphan and primary parameters $AUC_{0-\infty}$ and C_{max} indicate very similar total and maximum exposure after administration of Test and Reference.

Bioequivalence of both medicinal products was confirmed by the results obtained for total dextrorphan. Confidence intervals of $AUC_{0-\infty}$and C_{max} are completely inside the acceptance criteria of 80 – 125 % normally pre-set for bioequivalence testing. Point estimates are 100.8 % for $AUC_{0-\infty}$and 97.9 % for C_{max}.

Safety results:

No drug-related, severe, serious or other significant adverse events were observed in this trial. The adverse events reported by 3 of the 18 subjects were of mild or moderate intensity and were resolved at the end of the trial.

Any influence of the treatment on laboratory values, vital sign values or electrocradiogram parameters was not observed. The tolerability was assessed as good for all subjects under both treatments.

Overall, single oral doses of 21 mg dextromethorphan hydrobromide monohydrate were safe and well tolerated in healthy male and female subjects who are extensive metabolisers of CYP 2D6.

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Conclusions:

This study was performed in order to compare relative bioavailabilities of orally administered syrup preparation in comparison to soft pastilles. Based on the findings summarised and discussed before the following conclusions can be drawn:

- Even though the in-vivo performance of oral dextromethorphan formulations can be compared with highest discriminative power based on results obtained for the parent compound, this procedure is significantly limited by the extremely low concentrations of this compound in plasma, especially in extensive metabolisers.
- However, bioavailability was appropriately characterised by results obtained for the major active metabolite dextrorphan in this study population. Data determined for the parent compound can be considered supportively and also be included into the evaluation.
- Plasma profiles determined for the active metabolite are superimposable for total dextrorphan and very similar for the unconjugated compound.
- Total exposure of both medicinal products tested in this study is equivalent as indicated by AUC-values determined for both, unconjugated and total dextrorphan.
- Due to high variability of C_{max}-values, bioequivalence of maximum exposure could not be concluded from results reported for unconjugated dextrorphan. However, positive BE assessment between pastilles and syrup was possible based on the findings obtained for total dextrorphan.
- Certain deviations as observed for the parent drug with higher profiles obtained for the soft pastilles should not be overvalued due to insufficiently precise characterisation of plasma profiles for this compound.

Based on these findings, both products, syrup and soft pastilles, perform very similarly in vivo. As indicated by the results obtained for the parent compound it cannot be excluded that absorption may occur slightly accelerated and – due to partially bypassing hepatic first pass metabolism - plasma concentrations may reach slightly higher levels after administration of the soft pastilles compared to the oral solution (syrup).

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Conclusions, cont.:

According to the results obtained for the major active metabolite dextrorphan such slight deviations potentially existing between both products do not impact the efficacy or safety of both drugs. Thus, results of this study indicate that both formulations, syrup and soft pastilles, exhibit appropriate bioavailability and can be considered therapeutically equivalent.

The safety results of this trial do not alter the current knowledge about the safety pharmacology of dextromethorphan products.