# 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***.

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| **Name of company:** Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:** Dulcolax® and Laxoberal® | | **EudraCT No.:** 2007-004407-36 | |
| **Name of active ingredient:** bisacodyl and sodium picosulfate | | **Page:** 1 of 5 | **Synopsis No.:** |
| **Module:** | | **Volume:** | |
| **Report date:** 09 FEB 2009 | **Trial No. / U No.:** 122.57 / U09-1080-03 | **Date of trial:** 04 FEB 2008 – 23 MAY 2008 | **Date of revision:** 10 NOV 2009 |



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| **Title of trial:** | Investigation of the pharmacokinetics of 10 mg bisacodyl (coated tablets) or 10 mg sodium picosulfate (drops) administered orally in healthy lactating females. |
| **Principal Investigator:** | [redacted] |
| **Trial sites:** | [redacted] The Netherlands |
| **Publication (reference):** | Data of this study have not been published |
| **Clinical phase:** | I |
| **Objectives:** | To investigate if bisacodyl (Dulcolax®) and sodium picosulfate (Laxoberal®) is excreted in breast milk of healthy lactating women after an oral administration of 10 mg once daily over a period of 8 days. |
| **Methodology:** | Open label, parallel group design in healthy lactating female subjects |
| **No. of subjects:** | |
| **planned:** | entered: 16 |
| **actual:** | enrolled: 16 |
| | Treatment bisacodyl:<br>entered, treated and analysed (for pharmacokinetics):8<br>Treatment sodium picosulfate:<br>entered, treated and analysed (for pharmacokinetics):8 |
| **Diagnosis and main criteria for inclusion:** | Healthy female subjects, age ≥18, who decided to stop lactation |
| **Test product:** | Coated tablet bisacodyl, 5 mg per tablet |
| | Sodium picosulfate drops, 7.5 mg/ml |
| **dose:** | 10 mg once daily |
| **mode of admin.:** | Oral |
| **batch no.:** | Bisacodyl 5 mg batch no: 719064 |
| | Sodium picosulfate 7,5 mg/ml. batch no: 731119A |

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| **Duration of treatment:** | Eight days (no drug administration on day 2) |
| **Criteria for evaluation:** | |
| **Efficacy / clinical pharmacology:** | Pharmacokinetic parameters for BHPM:<br>After the first dose: $C_{max}$, $t_{max}$, $AUC_{\tau}$, $AUC_{0-\infty}$, $AUC_{0-tz}$, $\%AUC_{tz-\infty}$, $\lambda_z$, $t_{1/2}$, $MRT_{po}$, CL/F, $V_z$/F, $Ae_{t1-t2}$, $fe_{t1-t2}$, $CL_{R,t1-t2}$ and $AUC_{\tau,milk}$, $Ae_{t1-t2,milk}$ (daily infant dosage - day 1), $fe_{t1-t2,milk}$ (percentage of maternal dosage - day 1); milk-to-plasma ratio (day 1), estimated daily infant dosage (day 1)<br>After the last of 7 doses: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{\tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $Vz/F_{,ss}$, $Ae_{t1-t2,ss}$, $fe_{t1-t2,ss}$, $CL_{R,t1-t2,ss}$ and $AUC_{\tau,milk,ss}$, $Ae_{t1-t2,milk,ss}$ (daily infant dosage at steady state), $fe_{t1-t2,milk,ss}$ (percentage of maternal dosage at steady state); milk-to-plasma ratio at steady state, estimated daily infant dosage at steady state |
| **Safety:** | Physical examination, vital signs (BP, PR, oral body temperature), 12-leads ECG, laboratory tests and adverse events. |
| **Statistical methods:** | Descriptive statistics for safety and PK endpoints were calculated |

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**SUMMARY – CONCLUSIONS:**

**Efficacy / clinical pharmacology results:**

In milk, all measurements of free (unglucuronidated) and total (sum of glucuronidated and unglucuronidated) BHPM following single and multiple daily oral administrations of 10 mg bisacodyl or 10 mg sodium picosulfate were below the limit of quantification. Thus, these present data suggest that neither BHPM nor its glucuronides are excreted in the milk of healthy lactating human females.

After repeated administration of 10 mg bisacodyl once daily steady state for total BHPM was reached on study day 5. Plasma concentrations at day 1 and at steady state started to increase after a lag phase of 4 and 3 hours, respectively, and maximum concentrations occurred approximately 1 hour later. Total BHPM did not accumulate following multiple doses of 10 mg bisacodyl once daily. About 12.0% of the bisacodyl dose were excreted as total BHPM in urine at steady state within the dosing interval and approximately 17% of the bisacodyl dose were excreted as total BHPM in urine within 48 hours following a single dose.

Following administration of 10 mg sodium picosulfate once daily steady state for total BHPM was achieved on study day 5. At day 1 and day 8 plasma concentrations started to increase after a lag phase of 4 and 5 hours, respectively. Maximum concentrations were reached approximately 4 to 5 hours later. The accumulation of total BHPM following multiple daily doses of 10 mg sodium picosulfate was low. About 13.3% of the sodium picosulfate dose were excreted as total BHPM in urine at steady state within the dosing interval and approximately 10.4% of the sodium picosulfate dose were excreted as total BHPM in urine within 48 hours following a single dose.

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**Safety results:**

A total of 15 subjects ( 93.8%) experienced at least 1 AE during the course of the study. For 5 (31.3%) subjects, AEs were reported during the screening phase. For 15 subjects (93.8%), AEs were reported during the treatment phase of the study. Of these, 7 subjects received bisacodyl and 8 subjects received sodium picosulfate. In the post treatment phase 2 subjects (12.5%) reported AEs.

Most of the AEs were of mild intensity, and a few were of moderate intensity. There were no AEs of severe intensity. None of the AEs resulted in premature discontinuation of the study participation. Nearly all subjects recovered from their AEs except subject [redacted] (nasopharyngitis), where the outcome was reported as follow-up sufficient. No serious or other significant adverse events or deaths occurred during the study.

Overall, at the system organ class (SOC) level, the most frequently reported AEs were gastrointestinal disorders (93.8% of all subjects) and nervous system disorders (56.3% of all subjects). It is known that while using bisacodyl or sodium picosulfate episodes of abdominal discomfort including abdominal cramps, diarrhoea and abdominal pain (which may be associated with nausea and/or vomiting) may occur.

The most frequently reported AEs during the study were abdominal pain (87.5% of the subjects in the bisacodyl group, 100% of the subjects in the sodium picosulfate group), diarrhoea (87.5% of the subjects in both treatment groups, each) and headache (50% of the subjects in the bisacodyl group, 25% of the subjects in the sodium picosulfate group). Abdominal pain as well as diarrhoea was drug-related in all cases,which could be expected, wheras headache was not drug-related in any of the cases.

In total, drug-related adverse events as assessed by the investigator, occurred in 15 subjects (7 subjects in the bisacodyl group and 8 subjects in the sodium picosulfate group).

One subject in the bisacodyl group reported dizziness, which was assessed as a drug-related AE by the investiagtor, along with not related AEs like headache and nasopharyngitis as well as abdominal distension, abdominal cramps and diarrhoea.

The drug-related gastrointestinal disorders reported in this study are expected when treating healthy volunteers with laxatives. However, no serious AEs and no other significant AEs (according to ICH E3) occurred during the study.

There was no AE due to clinically relevant deviations in any of the laboratory parameters or due to ECG abnormalities. In general, there were no clinically relevant changes in the laboratory values compared to baseline. The monitoring of vital signs and the interpretation of ECG recordings did not reveal any safety concerns.

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**Conclusions:**

Neither repeated administration of 10 mg bisacodyl once daily nor repeated administration of 10 mg sodium picosulfate once daily to healthy female volunteers lead to the excretion of free (unglucuronidated) BHPM or total (sum of glucuronidated and unglucuronidated) BHPM into human milk. Total BHPM did not accumulate following multiple dosing of 10 mg bisacodyl and total BHPM accumulation after multiple doses of 10 mg sodium picosulfate was low. Less then 20.0% of the dose of either bisacodyl or sodium picosulfate were excreted as metabolites in urine at steady state during the dosing interval.

Neither repeated administration of 10 mg bisacodyl once daily nor repeated administration of 10 mg sodium picosulfate once daily lead to the excretion of free (unglucuronidated) BHPM or total (sum of glucuronidated and unglucuronidated) BHPM into human milk. Total BHPM did not accumulate following multiple dosing of 10 mg bisacodyl and total BHPM accumulation after multiple doses of 10 mg sodium picosulfate was low. Less then 20.0% of the dose of either bisacodyl or sodium picosulfate were excreted as metabolites in urine at steady state during the dosing interval.

A total of 15 subjects (93.8%) experienced at least one adverse event during the treatment phase of the study, 87.5% of the subjects in the bisacodyl group and 100% of the subjects in the sodium picosulfate group. All of these subjects experienced mild abdominal pain and nearly all of these subjects mild to moderate diarrhoea, which was assessed to be drug-related by the investigator. The drug-related gastrointestinal disorders reported in this study are expected when treating healthy volunteers with laxatives. For one subject in the bisacodyl group drug-related dizziness was reported. This AE occurred along with headache and nasopharyngitis as well as abdominal distension, abdominal cramps and diarrhoea. No serious or other significant adverse events or adverse events leading to discontinuation of the study participation occurred during the study. No clinically relevant changes in laboratory values, vital signs or ECG data from baseline were detected in both treatment groups.