## 1 Title Page

**Clinical Study Report No. 268/2005**  
Version 1.0

<table>
<thead>
<tr>
<th>Title</th>
<th>Version date: 09-May-2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title: Pharmacokinetics and relative bioavailability of Pantoprazole-Magnesium-Dihydrate 80 mg enteric-coated pellets under fed and fasted conditions and of the Pantoprazole-Sodium Sesquihydrate 40 mg tablet under fasted condition in healthy volunteers</td>
<td>INN: Pantoprazole</td>
</tr>
</tbody>
</table>
| Project No. / List No.: BY1023 | Compound No.: BYK79286 (Pantoprazole-Mg)  
BYK17374 (Pantoprazole-Na) |
| Batch No.: 340010 (Pantoprazole-Mg pellets)  
236960 (Pantoprazole-Na tablet) | Development phase: I |
| Study Protocol No.: BY1023/CP-078 | Indication studied: healthy subjects |
| EudraCT No: 2005-000816-28 | Date of early termination: not applicable |
| Study initiation date: 24-May-2005 | Study completion date: 15-Jun-2005 |
| Study completion date: 15-Jun-2005 | Summary of modifications: not applicable |

### Principal investigator:

PPD

### Name of sponsor's responsible medical officer:

PPD

### Person(s) responsible for study report:

PPD

### Sponsors contact persons:

See accompanying letter of the regulatory approval application

### Statement of GCP compliance:

This study was performed in accordance with Good Clinical Practice regulations as set forth in the ICH Consolidated Guideline E6 (CPMP/ICH/135/95)

### Archiving responsibility for essential documents:

Department RCD/CP at ALTANA Pharma AG and investigator according to ICH Consolidated Guideline E6.

This report is strictly confidential. Disclosure of contents to third parties is not permitted except by written consent of ALTANA Pharma AG, 78467 Konstanz, Germany.

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2 Synopsis

Title of the study: Pharmacokinetics and relative bioavailability of Pantoprazole-Magnesium-Dihydrate 80 mg enteric-coated pellets under fed and fasted conditions and of the Pantoprazole-Sodium Sesquihydrate 40 mg tablet under fasted condition in healthy volunteers

Principal investigator:

Study center:

Publication (reference): Not applicable

Studied period (years):
24 May 2005 – 15 June 2005

Clinical phase: I

Objectives:

Primary objective:
The primary objective of the study was to assess the pharmacokinetic characteristics AUC$\text{t}$ and $C_{\text{max}}$ as rate and extent characteristics of absorption of pantoprazole after single-dose administration of 80 mg pantoprazole-Mg (encapsulated enteric-coated pellets under fed and fasted conditions) and 40 mg pantoprazole-Na (enteric-coated tablet under fasted conditions) in healthy male volunteers. A comparison of the Mg-pellets and the Na-tablet, both in the fasted state, should give information on the influence of the salt form, formulation and dose on the pharmacokinetics of pantoprazole. A comparison of the pantoprazole-Mg pellets in the fed and fasted state should provide information on the potential influence of food on the pharmacokinetics of the pantoprazole-Mg encapsulated enteric-coated pellets.

Secondary objectives:
- To assess further pharmacokinetic characteristics: $AUC_{\text{inf}}$, $t_{1/2}$, $t_{\text{max}}$ and $t_{\text{lag}}$
- To evaluate safety and tolerability: adverse events, vital signs (non-invasive blood pressure, pulse rate), ECG, clinical laboratory
Methodology:

This monocenter study was conducted in healthy male volunteers according to a single-dose, open-label, randomized design. The study consisted of a screening examination, 3 treatment periods and a post-study examination. Subjects were randomized to six treatment sequences (balanced latin square) with a three-period change-over and a washout interval of 3 days between doses. On Study Day 1 of each treatment period all subjects received 80 mg pantoprazole-Mg or 40 mg pantoprazole-Na as a single oral morning dose. Pantoprazole-Mg was administered under fed or fasted conditions as encapsulated enteric-coated pellets; pantoprazole-Na was administered under fasted conditions as tablet with current enteric coating.

Serial blood samples were drawn for pharmacokinetic purposes at the following time points: pre-dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 7.5 h, 8 h, 9 h, 10 h, 11 h, 12 h, 14 h, and 24 h post-dose under fasted or fed conditions.

Analytical method: validated High Performance Liquid Chromatography (HPLC)-method with tandem mass spectrometric (MS/MS) detection equipped with an atmospheric pressure photoionization (APPI) source. The lower limit of quantitation (LLOQ) was 0.02 mg/L. The calibration range of the method was from 0.02-20.0 mg/L.

No. of subjects (total and for each treatment):

In total, 26 healthy male subjects entered the study: 24 of them received study medication according to the study protocol. The other two subjects were excluded before intake of study medication for safety reasons, as their blood pressure was high.

Diagnosis and criteria for inclusion:

Healthy male subjects, aged 18 and 55 years (inclusive), who gave their written informed consent and had a normal body weight (18 ≤ Body Mass Index ≤ 29 kg/m² and body weight > 60 kg).

Test product:

Pantoprazole-Mg encapsulated enteric-coated pellets.

Dose and mode of administration:

Single morning dose of 80 mg administered orally under fed and fasted conditions.
Batch No.: 340010

Duration of treatment:
1 day (single dose) under fed conditions and 1 day (single dose) under fasted conditions.

Reference product:
Pantoprazole-Na enteric-coated tablet.

Dose and mode of administration:
Single morning dose of 40 mg administered orally under fasted conditions.

Batch No.: 236960

Duration of treatment:
1 day (one single dose under fasted conditions).

Criteria for evaluation:
- **Primary pharmacokinetic variables:** the area under the plasma concentration-time curve until the last measured time point ($\text{AUC}_t$) and maximum plasma concentration ($\text{C}_{\text{max}}$) as respective extent and rate characteristics of pantoprazole.

- **Secondary pharmacokinetic variables:** the area under the plasma concentration-time curve extrapolated until infinity ($\text{AUC}_{\text{inf.}}$), apparent terminal elimination half-life ($t_{1/2}$), the time to reach the maximum plasma concentration ($t_{\text{max}}$) of pantoprazole and the lag-time ($t_{\text{lag}}$) as the time from administration until the last time point with concentrations below the lower limit of quantitation.

**Secondary safety variables:** Adverse events (AEs), laboratory work-up (blood chemistry, hematology, coagulation, urinalysis), physical examination, blood pressure (BP), pulse rate, body temperature, and 12-lead ECG (including heart rate, PR-, QRS-, RR, QT-, and QTc-interval).
Statistical methods:
Evaluation of the pharmacokinetic characteristics of pantoprazole and biostatistical analysis were performed using the validated programs WinNonlin (Version 4.1) and KINTPC (Version 2.1).

The AUC_t was calculated by the trapezoidal formula up to the last sampling time with a concentration above the lower limit of quantitation. AUC_inf. was calculated by extrapolation of AUC_t to infinity using standard techniques. Maximum plasma concentrations (C_max) and the times of their occurrence (t_max) were directly obtained from the plasma concentration-time profiles. The apparent terminal elimination half-life (t_1/2) was evaluated by t_1/2 = ln2/λ_z, where λ_z denotes the corresponding rate constant estimated by log-linear regression. The last of the initial time points with concentrations below the lower limit of quantitation was used as t_lag.

Ratio analysis (ANOVA) was performed for the primary pharmacokinetic characteristics AUC_t and C_max to compare 80 mg pantoprazole-Mg encapsulated enteric-coated pellets under both fasted and fed conditions with the 40 mg pantoprazole-Na enteric-coated tablet under fasted conditions. Likewise, an analysis of variance was performed for the secondary characteristics AUC_inf., t_1/2, t_max and t_lag. Corresponding comparisons were also made for the 80 mg pantoprazole-Mg encapsulated enteric-coated pellets in the fed state vs. the fasted state. The latter was done to investigate a potential food effect on the pharmacokinetics of the pantoprazole-Mg encapsulated enteric-coated pellets. With the exception of t_max and t_lag, for which an additive model was chosen (no logarithmic transformation), the pharmacokinetic characteristics were investigated by using a multiplicative model and parametric analysis. Point estimates and 90% confidence intervals (CI) were given for the Test/Reference ratios of the population medians for the multiplicative models and for the difference Test – Reference of population means for the additive models.

The safety variables were analyzed descriptively, including summary statistics (e.g. median, min and max, 68%-range, mean, SD) where appropriate.

SUMMARY - CONCLUSIONS
Demographic data:
A total of 26 subjects were included in the study; all were of Caucasian origin. Of these, 24 subjects received two single oral doses of 80 mg pantoprazole-Mg and one single oral dose of 40 mg pantoprazole-Na according to the study protocol. Median [min, max] value for their age was 36 [23, 51] years, for body weight was 74.5 [62, 99] kg, and for height was 175 [170, 191] cm.
Pharmacokinetic results:
The point estimates (90% CI) of the AUC_t- and C_max-ratios (primary variables, dose-normalized) for the comparison of the 80 mg pantoprazole-Mg encapsulated enteric-coated pellets with the 40 mg pantoprazole-Na enteric-coated tablet, both in the fasted state, were 81.6% (75.5, 88.3%) and 55.3% (48.0, 63.7%), respectively. The corresponding AUC_t- and C_max-ratios for the comparison of 80 mg pantoprazole-Mg encapsulated enteric-coated pellets in the fed state vs. the 40 mg pantoprazole-Na enteric-coated tablet in the fasted state were 65.1% (57.0, 74.4%) and 36.7% (29.3, 46.0%), respectively. Considering the bioequivalence range of 80-125% for AUC_t and C_max the 80 mg pantoprazole-Mg encapsulated enteric-coated pellets (either fed or fasted) after dose normalization would not have been bioequivalent to the 40 mg pantoprazole-Na enteric-coated tablet (fasted), if bioequivalence had been tested for. The considerably lower C_max observed for the 80 mg pantoprazole-Mg encapsulated enteric-coated pellets are probably due to both the inherent properties of the multiparticulate pellet formulation in comparison to the monolithic tablet and the slower dissolution rate of the pantoprazole-Mg salt compared to pantoprazole-Na.

The potential influence of food on the bioavailability of the pantoprazole-Mg pellet formulation was also investigated. The point estimates (90% CI) of the AUC_t- and C_max-ratios for the comparison of 80 mg pantoprazole-Mg encapsulated enteric-coated pellets in the fed vs. the fasted state were 79.8% (68.2, 93.3%) and 66.5% (54.7, 80.8%), respectively. Again, the pantoprazole-Mg encapsulated enteric-coated pellets in the fed and the fasted state would not have been bioequivalent if bioequivalence had been tested for. Based on these results, the presence of a food effect on the pharmacokinetics of the 80 mg pantoprazole-Mg encapsulated enteric-coated pellets is apparent.

The considerably decreased C_max of the pantoprazole-Mg encapsulated enteric-coated pellets after the intake of a critically high-fat, high-caloric breakfast may be partially explained by the occurrence of double plasma peak concentrations or otherwise irregularly shaped profiles in a considerable number of subjects in the fed state when compared to the fasted state, where profiles were mostly regularly shaped. The AUC of the pantoprazole-Mg encapsulated enteric-coated pellets was also lowered by food, contributing to the decrease in C_max. The reason for the decrease of the AUC in the fed state is unclear. Some of the encapsulated enteric-coated pellets might have been carried to deeper sections of the intestines by the food before dissolution occurred, thus missing the optimum absorption window. Another reason could be fluctuations of the pH in the duodenum caused by the intense digestion process leading to some slightly acidic episodes followed by partial degradation of pantoprazole.
Point estimates (90%-confidence intervals) for the Test/Reference ratios of $AUC_t$, $C_{\text{max}}$ (dose-normalized) and $t_{\text{max}}$ of pantoprazole: 80 mg pantoprazole-Mg pellets (fasted or fed) vs. 40 mg pantoprazole-Na tablet (fasted) and 80 mg pantoprazole-Mg pellets, fed vs. fasted state

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference</th>
<th>Dependent</th>
<th>Point Estimate</th>
<th>90%-CI</th>
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<tr>
<td>Mg-pellets 80 mg</td>
<td>Na-tablet</td>
<td>$AUC_t$</td>
<td>81.6</td>
<td>75.5 - 88.3</td>
</tr>
<tr>
<td>Mg-pellets 80 mg</td>
<td>40 mg</td>
<td>$C_{\text{max}}$</td>
<td>55.3</td>
<td>48.0 - 63.7</td>
</tr>
<tr>
<td>Mg-pellets 80 mg</td>
<td>Mg-pellets</td>
<td>$t_{\text{max}}$</td>
<td>-0.83 $^1$</td>
<td>n.a. - n.a.</td>
</tr>
<tr>
<td>fed</td>
<td>fed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg-pellets 80 mg</td>
<td>Na-tablet</td>
<td>$AUC_t$</td>
<td>65.1</td>
<td>57.0 - 74.4</td>
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<tr>
<td>Mg-pellets 80 mg</td>
<td>40 mg</td>
<td>$C_{\text{max}}$</td>
<td>36.7</td>
<td>29.3 - 46.0</td>
</tr>
<tr>
<td>Mg-pellets 80 mg</td>
<td>Mg-pellets</td>
<td>$t_{\text{max}}$</td>
<td>2.54 $^1$</td>
<td>n.a. - n.a.</td>
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<tr>
<td>fed</td>
<td>fed</td>
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</tbody>
</table>

$^1$ difference between Test and Reference (h)  
n.a.: not available

Safety results:
Two randomized subjects were withdrawn during baseline (prior to the first intake of study medication) due to safety concerns. During treatment, a total of 22 AEs were reported by 9 (38%) subjects. The reported AEs were in general mild or moderate in intensity, and they resolved completely in all cases. The most frequently reported treatment-emergent AEs were headaches, which occurred in 6 subjects. None of the events were classified as unexpected or serious AEs. None of the treatment-emergent AEs led to study discontinuation.

Laboratory values did not show any clinically relevant changes between the screening and post-study examination. After intake of the study medication, no clinically relevant alterations were observed during physical examination (including ECG and vital signs).

Overall, the safety data obtained in the present study indicate that oral administration of 80 mg pantoprazole-Mg encapsulated enteric-coated pellets and 40 mg pantoprazole-Na enteric-coated tablet is safe.

Conclusions:
The dose-normalized $AUC_t$ and $C_{\text{max}}$ of the 80 mg pantoprazole-Mg encapsulated enteric-coated pellets were 81.6% and 55.3%, respectively, of the 40 mg pantoprazole-Na enteric-coated tablet, both in the fasted state. Corresponding values for the 80 mg pantoprazole-Mg pellets in the fed state vs. the 40 mg pantoprazole-Na tablet in the fasted state were 65.1% and 36.7%, respectively. The lower $C_{\text{max}}$ for the 80 mg pantoprazole-Mg pellets is probably due to both the inherent properties of the multiparticulate pellet formulation in comparison to the monolithic tablet and to the slower dissolution rate of the pantoprazole-Mg salt compared to
pantoprazole-Na. AUC_{t} and C_{max} of the 80 mg pantoprazole-Mg pellets in the fed vs. the fasted state were 79.8% and 66.5%, respectively, indicating the presence of a food effect. The safety profiles of the two pantoprazole-salt formulations are comparable.