# 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.

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# 3. SYNOPSIS AND TRIAL ABSTRACT

## 3.1 SYNOPSIS

| | | | | |
|---|---|---|---|---|
| **Name of company:** Boehringer Ingelheim Pharma KG | | **Tabulated Study Report** | | **(For National Authority Use only)** |
| **Name of finished product:** Not applicable | | | | |
| **Name of active ingredient:** DAU 6215 CL, Itasetron | | **Page:** | **Number:** | |
| **Ref. to Documentation:** | **Volume: I** | **Page: 1** | **to SDL 73** | **Addendum No.:** |
| **Report date:** 05 February 1999 | **Number:** 208.629 | **Study period (years):** 3/98 – 5/98 | | |

| | |
|---|---|
| **Title of study:** | Investigation of the effects of food on the bioavailability and pharmacokinetic profile of Itasetron after a single oral dose of 1 mg in healthy male subjects (3-way cross-over). |
| **Investigators:** | [redacted] |
| **Study centre(s):** | Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma KG, F.R.G. |
| **Publication (reference):** | not applicable |
| **Clinical phase:** | I |
| **Objectives:** | effects of food on the absolute and relative bioavailability, pharmacokinetic profile, safety and tolerability |
| **Methodology:** | intraindividual cross-over comparison of three treatments, randomised, open-labelled |
| **No. of subjects entered:** | |
| **total:** | 15 |
| **each treatment:** | Itasetron 1 mg tablet oral after a "high fat" breakfast -15; Itasetron 1 mg tablet oral -15; Itasetron 2.5 mg i.v. –15 |
| **Diagnosis and main criteria for inclusion:** | healthy male volunteers, age 21 – 50 years, Broca-Index: ± 20 % |
| **Test product:** | Itasetron |
| **dose:** | 1 mg |
| **mode of admin.:** | oral - film-coated tablet, single dose after a standardised "high fat" breakfast |
| **batch no.:** | 715454 |
| **Duration of treatment:** | one day at each treatment |
| **Reference therapy:** | Itasetron |
| **dose:** | 1 mg |
| **mode of admin.:** | oral – film-coated tablet, single dose, subjects in a fasted state |
| **batch no.:** | 715454 |
| **Reference therapy:** | Itasetron |
| **dose:** | 2.5 mg (ampoule containing 2.5 mg/2.5 ml) Itasetron |
| **mode of admin.:** | intravenous infusion (15 min), test product in 20 ml saline (0.9 % NaCl), subjects in a fasted state single dose |
| **batch no.:** | 9604201 |

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|---|---|---|---|
| **Name of company:** Boehringer Ingelheim Pharma KG | | **Tabulated Study Report** | **(For National Authority Use only)** |
| **Name of finished product:** Not applicable | | **SUPPLEMENTARY SHEET** | |
| **Name of active ingredient:** DAU 6215 CL, Itasetron | | **Page:** **Number:** | |
| **Ref. to Documentation:** | **Volume:** I | **Page:** 1 **to** SDL 73 | **Addendum No.:** |
| **Report date:** 05 February 1999 | **Number:** 208.629 | **Study period (years):** 3/98 – 5/98 | |

**Criteria for evaluation:**

**Safety:** Blood pressure, pulse rate, ECG, laboratory parameters, adverse events

**Pharmacokinetics:** Pharmacokinetic parameters: $AUC_{0-\infty}$, $C_{max}$ (all treatments), $t_{max}$, $AUC_{0-tlast}$, $C_{max}/AUC$, $MRT_{tot}$, $t_{½}$, $V_z/f$, $CL_{tot}/f$ (oral treatments), $MRT_{tot}$, $t_{½}$, $V_z$, $V_{ss}$, $CL_{tot}$ (intravenous administration)

**Statistical methods:** descriptive summary statistics, 95 % confidence intervals (absolute bioavailability), two one-sided t-tests procedure (relative bioavailability)

**SUMMARY – CONCLUSIONS:**

Pharmacokinetics:
The trial drug was administered to 15 healthy male subjects as a 1 mg film-coated tablet in fasted state, as a single 1 mg film-coated tablet after a standardised "high fat" breakfast and as an intravenous infusion of 2.5 mg/20 ml over 15 min in fasted state (three way cross-over). Itasetron plasma concentrations were assayed in terms of the free base by specific and validated HPLC-MS/MS methods reported in U97-2267. Geometric means of non-compartmental pharmacokinetic parameters as obtained within three treatment groups are summarised below:

TABLE 1: Summary Statistics of Pharmacokinetic Parameters of Itasetron Derived from Plasma Concentration-Data by Noncompartmental Methods After Administration of 1 mg Itasetron as Tablet in Fasted and in Fed State as well as 2.5 mg Itasetron as Intravenous Infusion, N = 15:

| | | 1 mg tablet in fasted state | | 1 mg tablet in fed state | | 2.5 mg/20 ml after i.v. infusion in fasted state | |
|---|---|---|---|---|---|---|---|
| parameter | unit | gmean | gCV (%) | gmean | gCV (%) | gmean | gCV (%) |
| $AUC_{0-\infty}$ | [ng·h/ml] | 33.7 | 17.0 | 35.9 | 21.6 | 85.4 | 17.8 |
| $AUC_{tf-\infty}$ | (%) | 4.58 | 40.5 | 5.05 | 60.9 | 4.14 | 47.5 |
| $C_{max}$ | [ng/ml] | 2.66 | 23.1 | 2.83 | 30.6 | 26.6 | 28.8 |
| $t_{max}$ | [h] | 1.0$^{\$}$ | - | 2.0$^{\$}$ | - | - | - |
| $t_{½}$ | [h] | 11.0 | 13.8 | 11.5 | 21.1 | 10.9 | 17.1 |
| $MRT_{tot}$ | [h] | 15.6 | 12.6 | 16.2 | 18.2 | 14.3 | 14.1 |
| $Cl_{tot}/f$; $Cl_{tot}$ | [ml/min] | 495 | 17.0 | 465 | 21.6 | 488 | 17.8 |
| $V_z/f$; $V_z$ | [l] | 473 | 18.6 | 464 | 18.9 | 462 | 20.3 |

source data: TABLEs 13: 4; 13: 5 and 13: 6

$^{\$}$median; all data are rounded to 3 significant digits

Absolute bioavailability of the 1 mg Itasetron film-coated tablets administered in fasted state and after a standardised "high fat" breakfast was investigated in comparison to the administration of 2.5 mg Itasetron as an intravenous infusion in fasted state for $AUC_{0-\infty}$ and for $C_{max}$. For $AUC_{0-\infty}$ an absolute bioavailability of 98.6 % in fasted state and of 105.0 % in fed state could be determined (TABLE 13.7).

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**SUMMARY – CONCLUSIONS:**

The relative bioavailability of the 1 mg Itasetron film-coated tablets administered after a standardised "high fat" breakfast was 106.5 % with confidence limits from 101.4 to 111.8 % ($CV_{intraindiv.}$ = 7.8 %) for $AUC_{0-\infty}$ and 106.6 % with confidence limits from 92.4 to 123.0 % and an intraindividual CV of 23.3 % due to $C_{max}$ in comparison to $AUC_{0-\infty}$ and $C_{max}$ values in the fasted state (TABLEs 9.4.3: 3 and 9.4.3: 4). A slight but not significant food effect could be determined.
For $t_{max}$ only one of the two tested one-sided null hypotheses can be rejected at the 5 % level of significance (cf. section 9.4.3). Therefore bioequivalence can not be concluded on the basis of $t_{max}$.

Safety results:

Itasetron was observed to be safe and systemically well tolerated within the three treatments. Eight mild adverse events in 5 subjects occurred (five subjects with "constipation", two subjects with "flatulence", one subject with "headache"). The absolute number of subjects with adverse events (infusion –3; tablet fasted –2; tablet fed –1) as well as the absolute number of adverse events (infusion –4; tablet fasted –2; tablet fed –2) was highest after the intravenous infusion of 2.5 mg Itasetron.

Conclusions:

The ingestion of a "high fat" meal prolonged $t_{max}$ of Itasetron 1 mg tablet slightly. Food administration had nearly no impact on geometric mean $AUC_{0-\infty}$ and $C_{max}$ values.
The pharmacokinetic investigation demonstrated a mean relative bioavailability of the tablet in fed state of 106.5 % due to $AUC_{0-\infty}$ values and of 106.6 % due to $C_{max}$ values compared to the tablet in fasted state.
The absolute bioavailability of both treatments was comparable in fed and in fasted state.

The slight food effect seen in few subjects in this study is unlikely to be of relevance regarding the administration of 1 mg Itasetron film-coated tablets in general clinical practice in this indication.

Itasetron was safe and well tolerated on all treatments. Five subjects reported 8 adverse events, all of them of mild intensity.