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Bioavailability and Bioequivalence of Two Enteric-Coated Formulations of Omeprazole in Fasting and Fed Conditions

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Abstract

Objective: To investigate the relative bioavailability and bioequivalence, in fasting and fed conditions, of repeated doses of two omeprazole enteric-coated formulations in healthy volunteers.

Material and methods: Open label, single-centre study consisting of two consecutive randomised, two-way crossover trials (a fasting trial and a fed trial). Each trial consisted of two 7-day treatment periods in which subjects received one daily dose of the test (Ompranyt®) or reference (Mopral®) formulations. At day 7 and day 14 (fasting trial), products were administered in fasting conditions and blood samples were taken for omeprazole plasma assay over 12 hours. At day 21 and day 28 (fed trial), products were administered after a standard high-calorie and high-fat meal and 12-hour blood samples taken. Omeprazole plasma concentrations were quantified by a validated method using a reverse-phase high performance liquid chromatography with UV detection (HPLC-UV).

Results: Twenty-four subjects were enrolled and 23 completed the study. Under fasting conditions, the mean ± SD maximum omeprazole plasma concentration (C_{max}) was 797 ± 471 μg/L for Ompranyt® and 747 ± 313 μg/L for Mopral® with a point estimate (PE) of 1.01 and a 90% confidence interval (CI) of 0.88, 1.16. The mean ± SD area under the plasma concentration curve from administration to last observed concentration (AUC_{0-12}) was 1932 ± 1611 μg • h/L and 1765 ± 1327 μg • h/L for Ompranyt® and Mopral®, respectively (PE = 1.09; 90% CI 0.95, 1.25). In the presence of food, the C_{max} was 331 ± 227 μg/L and 275 ± 162 μg/L (PE = 1.21; 90% CI 0.92, 1.59) and AUC_{0-12} was 1250 ± 966 μg • h/L and 1087 ± 861 μg • h/L (PE = 1.16; 90% CI 0.92, 1.47) for Ompranyt® and Mopral®, respectively. Bioequivalence of the formulations in the fasting condition was demonstrated both for AUC_{0-12} and for C_{max} because the 90% CI lay within the acceptance range of 0.80–1.25. In contrast with the fasting condition, there were significant reductions in rate (C_{max}) and extent (AUC_{0-12}) of systemic exposure when test and reference formulations were administered with food. The food effect was more marked with Mopral® than with Ompranyt®, and the bioequivalence criterion was not fulfilled because the 90% CI fell out of the accept-

ance range of 0.80, 1.25, for both C_{max} and AUC_{0-12}. The two formulations were similarly well tolerated.

Conclusion: Bioequivalence of Ompranyt® (test formulation) and Mopral® (reference) formulations was demonstrated after repeated dosing in the fasting condition. Following a high-calorie and high-fat meal, there was a significant reduction in rate and extent of systemic exposure for both products, with Ompranyt® being less affected than Mopral® by the presence of food.

Proton pump inhibitors (PPIs) are one of the most frequently used pharmacological classes. The first PPI to reach the market was omeprazole, which is indicated for the treatment of duodenal and gastric ulcers, gastro-oesophageal reflux disease, erosive oesophagitis, hypersecretory conditions and, in combination with antimicrobial agents, eradication of *Helicobacter pylori* infection.

The PPIs selectively and irreversibly inhibit the gastric H^+/K^+-exchanging ATPase ('proton pump'). Inactivation of this enzyme system blocks the final step of acid secretion by parietal cells, inhibiting both basal and stimulated secretion of gastric acid independently of the nature of stimulation.[1] Omeprazole, similar to other PPIs, does not directly inhibit this enzyme system, but instead concentrates in the acid conditions of the parietal cell secretory canaliculi, where it undergoes rearrangement to its active sulphenamide metabolite. This metabolite then reacts with sulfhydryl groups of H^+/K^+-exchanging ATPase, inactivating the proton pump. Because the sulphenamide metabolite forms an irreversible covalent bond with the proton pump, acid secretion is inhibited until new enzyme molecules are synthesised, resulting in a prolonged duration of action (48–72 hours).[2]

BIAL SA owns a marketing authorisation for Ompranyt® [1] in several countries, and the aim of the present study was to investigate the bioequivalence of this formulation of omeprazole in relation to the reference formulation (Mopral®, AstraZeneca, Madrid, Spain – Spanish brand name for the omeprazole formulation internationally known as Losec®, Prilosec®, etc.).

Since omeprazole and the other PPIs are all acid-labile, they must be protected from intragastric acid when given orally. This is achieved by the use of enteric-coated formulations, but differences in coating may influence protection against the acid and, consequently, may affect bioavailability. Both Ompranyt® and Mopral® are formulated as enteric-coated pellets in hard gelatine capsules. Typically, coating is intended to delay the release of drug until it has passed through the acidic medium of the stomach, and the enteric-coated formulations are classified as 'modified-release products'.[3] For oral 'modified-release' generic products, both the US FDA and European Medicines Agency (EMEA) recommend bioequivalence assessment in fasting and fed conditions.[4,5] In this study, therefore, bioequivalence of test and reference formulations was assessed in fasting conditions and following a standard meal.

The PPI class represents a special case in which the pharmacodynamic effect (gastric acid suppression with subsequent pH increase) may affect drug absorption and bioavailability. The oral bioavailability of omeprazole is initially low (approximately 35–40%) but increases to about 65% in the first 3–5 days of administration.[6,7] The most likely explanation for this phenomenon is that omeprazole absorption increases with repeated dosing because less omeprazole is degraded once acid secretion is inhibited, leaving more compound available for absorption.[1] Because of the increase in bioavailability of omeprazole following repeated dosing, this study will determine the relative bioavailability of test and reference formulations after the inhibition of the proton pumps. This procedure is in agreement with

1 The use of trade names is for product identification purposes only and does not imply endorsement.

the recommendations by the EMEA[8] for the assessment of bioequivalence of drug products with time-dependent pharmacokinetics and by the Committee for Evaluation of Medicines for Human Use (CODEM) of the Spanish Medicines Agency with respect to the specific case of bioequivalence studies with omeprazole.[9]

The elimination half-life of omeprazole after oral administration has been estimated at about 1 hour, and approximately 8 hours later the serum concentrations of omeprazole are usually below the limit of detection.[1] Therefore, a 12-hour sampling coverage was considered to be appropriate for omeprazole plasma assay. In most healthy subjects given omeprazole 10–60mg, peak plasma omeprazole concentrations were achieved by 1–1.5 hours, although marked variation in individual peak concentrations were seen.[1] These data indicate the need for short sampling time intervals in the first hours after dosing.

The omeprazole dose strength usually recommended for the treatment of peptic ulcers, gastroesophageal reflux disease and *H. pylori* infection is 20mg. Therefore, the 20mg strength was chosen for this study.

This was an open-label, single-centre study consisting of two consecutive randomised, two-period, two-way crossover trials (part 1 – fasting trial and part 2 – fed trial; figure 1). Each part consisted of two sequential 7-day treatment periods in which subjects were randomly assigned to once-daily treatment with either Ompranyt® or Mopral® during the first period and the alternative formulation during the second one. The study products were administered following an overnight fast of at least 10 hours on days 7 and 14 (fasting trial), and following the ingestion of a high-calorie and high-fat breakfast on days 21 and 28 (fed trial). Following product administration on those days, blood samples for omeprazole plasma assay were taken over 12 hours. No washout periods were scheduled between treatment periods, which is considered an acceptable procedure since the pharmacokinetic assessments were performed after the administration of multiple doses. A similar procedure has been adopted by Richards et al.[10]

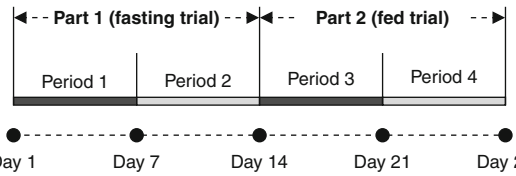

Fig. 1. Schematic representation of the study design. **Part 1:** randomised, two-period, two-sequence crossover trial under fasting conditions; **part 2:** randomised, two-period, two-sequence crossover trial under fed conditions; **day 1:** randomisation and start of product administration; **day 7:** 12-hour blood sampling and crossing-over; **day 14:** 12-hour blood sampling and completion of part 1; **day 21:** 12-hour blood sampling and crossing-over; **day 28:** 12-hour blood sampling and completion of the study. Screening took place within the 2-week period prior to randomisation. A follow-up visit took place 1 week after study completion.

The study was conducted by the Human Pharmacology Unit of BIAL (S. Mamede do Coronado, Portugal) operating at the facilities of the Hospital Santa Maria, Porto, Portugal. An independent Ethics Committee revised and approved the study protocol and the information provided to the volunteers. Subjects' written informed consent was obtained prior to enrolment in the study. The study was conducted according to the principles of the Declaration of Helsinki and the International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines. Bioanalytical analyses were conducted at the Laboratory of Pharmacological Research of BIAL (S. Mamede do Coronado, Portugal) in accordance with Good Laboratory Practice (GLP) guidelines.

A total of 24 healthy volunteers (12 males and 12 females), aged between 18 and 55 years, with a body mass index between 19 and 28 kg/m^2 and who met the inclusion and exclusion criteria, were enrolled in the study. Taking into account the reported variability of omeprazole plasma concentrations[1,10-15] and assuming a within-subject variance (σ_{WT}) of ≤0.23, a sample size of 24 subjects allowed detection of a variation of 5% ($\Delta = 0.05$) between the two formulations with a power of 80%.[16]

Volunteers were subjected to the following pre-study screening: clinical history; physical examination; HIV-1, HIV-2, hepatitis B and hepatitis C serology; drugs of abuse screen; haematology, plas-

ma biochemistry and urinalysis; 12-lead ECG; and pregnancy test in women.

Subjects were excluded from participation if they had one or more of the following: a history of abnormal drug reactions or drug allergies; hypersensitivity or any other contraindication to omeprazole; blood donation within 3 months prior to screening; medication with any 'over-the-counter' (OTC) or prescribed drug within 1 week prior to the study; cigarette smokers (>10 cigarettes per day); evidence of chronic drug abuse (including alcohol); positive tests for surface hepatitis B antigen (HBsAg) or hepatitis C, HIV-1 or HIV-2 antibodies; and positive test for drugs of abuse (phencyclidine, barbiturates, benzodiazepines, methamphetamine, cocaine, cannabis, amphetamine and opioids). Because studies in Asian subjects receiving single omeprazole 20mg doses show an approximately 4-fold increase in the area under the plasma concentration versus time curve (AUC) compared with Caucasian subjects,[17] Asian subjects were not admitted to the study. No medication other than study products and oral contraceptives was allowed to be taken within 8 hours of administration of study products. Seven (58.3%) women included in the study were using oral contraceptives.

The following products were used: Ompranyt® 20mg capsules (Laboratórios BIAL – Portela & Cª SA, S. Mamede do Coronado, Portugal), and Mopral® capsules 20mg (Astra Production, Sodertalje, Sweden; marketed by AstraZeneca, Madrid, Spain).

In each part of the study, each subject received one Ompranyt® 20mg capsule daily over 7 consecutive days, and one Mopral® 20mg capsule daily for a further 7 days. The order of product was determined by randomisation.

On the first 6 days of each period, subjects reported to the research facilities early in the morning (between 0800h and 0900h) to receive the study product under supervision of the investigation staff. Subjects completed a brief history each day, prior to administration of the study product, to ensure that no adverse events had developed since the previous visit. Subjects were randomly subjected to urine tests for drugs of abuse. On the blood sampling days (days 7, 14, 21 and 28), subjects were admitted on the evening of the day before and remained in the research facilities until at least the 12-hour post-dose blood samples had been taken. On the night before days 7, 14, 21 and 28, subjects were requested to fast from 2200h.

On days 7 and 14 (part 1, fasting trial), between 0800h and 0900h, a cannula was inserted in a forearm vein, the first (pre-dose) blood sample was collected, and the study product was administered. The subjects remained fasted until 4 hours following product administration.

On days 21 and 28 (part 2, fed trial), between 0800h and 0900h, a cannula was inserted in a forearm vein, a standard high-calorie and high-fat breakfast was eaten, the first (pre-dose) blood sample was collected, and the study product immediately administered. The standard meal consisted of 1 unit of cereal with whole milk, two scrambled eggs, two grilled strips of bacon, one croissant, one slice of toast with one part of butter, and non-citrus juice. The caloric content corresponded to approximately 750 kcal (with fat corresponding to approximately 50% of total caloric content). No other food was allowed until 4 hours post-dose.

The study products were ingested with 200mL of water. A standardised lunch, snack and dinner were served at the same time in each period of the study (4, 7 and 10 hours post-dose, respectively). Water *ad libitum* was allowed except for 1 hour before and 1 hour after drug administration.

There were no special diet recommendations prior to the study. During the study, subjects were requested to refrain from consuming alcohol or xanthine-containing beverages, smoking and performing intense physical activities. No alcohol and grapefruit- or citrus-containing beverages were allowed from the time of admission to the research facilities until 12 hours post-dose.

On days 7, 14, 21 and 28, 7mL blood samples were collected for omeprazole assay at the following time-points: pre-dose, at 20 and 40 minutes, and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose. Blood samples were drawn into 7mL Vacutainer®

tubes containing heparin-lithium as anticoagulant and centrifuged at 3000*g* for 10 minutes at 4ºC. Two 1mL plasma aliquots were prepared and frozen at approximately –80ºC until analysis.

Adverse events were assessed by spontaneous reporting and direct questioning of the study subjects at the time of daily product administration. All adverse events were assessed regarding the type, duration, intensity, severity, outcome and treatment relationship (causality).

Plasma sample preparation was achieved by solid-phase extraction (SPE). Omeprazole levels were quantified by reverse-phase high performance liquid chromatography (HPLC) with UV detection, using a previously validated method.[15] The limit of quantification was 25 μg/L.

The following omeprazole pharmacokinetic parameters were derived by non-compartmental analysis from the plasma concentration versus time profiles using WinNonlin (version 4.0, Pharsight Corporation, Mountain View, CA, USA): maximum observed plasma drug concentration (C_{max}) post-dose, time of occurrence of C_{max} (t_{max}), and AUC from time zero to the last sampling time at 12 hours (AUC_{0-12}), calculated by the linear trapezoidal rule.

According to various regulatory bodies,[3-8] the statistical method for testing bioequivalence should be based upon a 90% confidence interval (CI) for the ratio of the population means (test/reference) for the parameters under consideration. This method is equivalent to the corresponding two 1-sided test procedures with the null hypothesis of bioinequivalence at the 5% significance level.[3,18] The analysis of variance (ANOVA) was used to evaluate AUC and C_{max}, and the data were transformed prior to analysis using a logarithmic transformation. Equivalence was accepted if the 90% CI was totally contained within the range 0.80–1.25. The ANOVA model for repeated measures with two factors (formulation and treatment sequence) was used. Once the value of residual variance had been obtained (from previous ANOVA), the 90% CI was calculated and the unilateral test of Schuirmann was performed. Finally, the Wilcoxon sum rank test was used to calculate t_{max}. Calculations were made using the Statistical Analysis System (SAS; release 8.2, SAS Institute Inc., Cary, NC, USA).

Results

Study Population

Twenty-four volunteers were enrolled but one female subject withdrew consent during the study and was not replaced. Among those 23 subjects who finished the study, 12 (52.2%) were male and 11 (47.8%) were female. All but one subject was Caucasian. The mean age ± SD of the study population was 26.0 ± 8.0 years (median 22.5; range 19–44), the mean weight was 66.1 ± 10.5kg (median 63.5; range 49–88), and the mean height was 169.0 ± 12.1cm (median 169.5; range 146–195).

Pharmacokinetic Parameters

The main pharmacokinetic parameters are summarised in table I, and mean omeprazole plasma concentration versus time profiles are shown in figure 2. Some subjects still had omeprazole plasma concentrations above the limit of qualification at the

Table I. Pharmacokinetic parameters of omeprazole following oral administration of Ompranyt® (test formulation) and Mopral® (reference) in fasting and fed conditions (n = 23)[a]

Formulation	Fasting			Fed		
	C_{max} (μg/L)	t_{max} (h)	AUC_{0-12} (μg • h/L)	C_{max} (μg/L)	t_{max} (h)	AUC_{0-12} (μg • h/L)
Ompranyt®	797 (471)	1.5 (1.0–3.0)	1932 (1611)	331 (227)	3.0 (1.0–10.0)	1250 (966)
Mopral®	747 (313)	1.0 (0.7–2.5)	1765 (1327)	275 (162)	4.0 (1.5–12.0)	1087 (861)

a C_{max} and AUC_{0-12} results are expressed as arithmetic mean with SD in parentheses; t_{max} values are presented as median with range in parentheses.

AUC_{0-12} = area under the plasma concentration-time curve (AUC) from time zero to the last sampling time at 12 hours; **C_{max}** = maximum observed plasma drug concentration; **t_{max}** = time of occurrence of C_{max}.

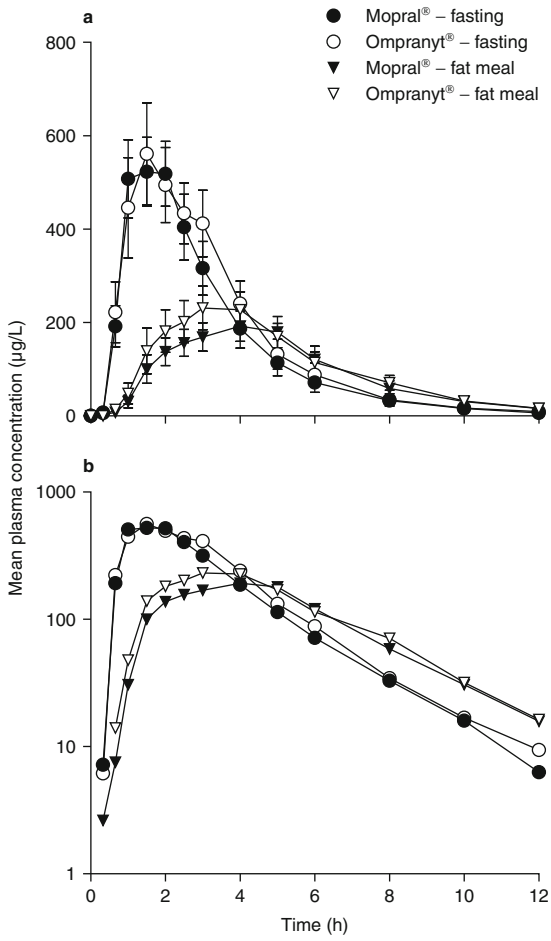

Fig. 2. Mean ± SEM plasma omeprazole concentration versus time profiles following administration of Ompranyt® (test formulation) and Mopral® (reference) in fasting and fed conditions (n = 23); (**a**) linear scale; (**b**) semilog scale.

last sampling time (12 hours). However, extrapolation of AUC over the dosing interval (24 hours) showed that $AUC_{0\text{-}12}$ represented at least 80% of the corresponding $AUC_{0\text{-}24}$.

Under fasting conditions, the arithmetic mean ± SD value of C_{max} was 797 ± 471 µg/L for Ompranyt® and 747 ± 313 µg/L for Mopral® with a geometric means ratio (point estimate [PE]) of 1.01 and a 90% CI of 0.88, 1.16 (table II). The mean ± SD $AUC_{0\text{-}12}$ was 1932 ± 1611 µg • h/L and 1765 ± 1327 µg • h/L for Ompranyt® and Mopral®, respectively, with a PE of 1.09 and a 90% of CI 0.95, 1.25. The median t_{max} was 1.5 hours (range 1.0–3.0) for Ompranyt® and 1.0 hours (range 0.7–2.5) for Mopral®. Compared with Mopral®, C_{max} with Ompranyt® occurred 0.5 hours later, but the difference did not achieve statistical significance (z = 1.4825, p = 0.1382).

In the presence of food, C_{max} was 331 ± 227 µg/L for Ompranyt® and 275 ± 162 µg/L for Mopral® with a PE of 1.21 and a 90% CI of 0.92, 1.59 (table II). $AUC_{0\text{-}12}$ was 1250 ± 966 µg • h/L for Ompranyt® and 1087 ± 861 µg • h/L for Mopral® with a PE of 1.16 and a 90% CI of 0.92, 1.47. Median t_{max} was 3.0 hours (range 1.0–10.0) for Ompranyt® and 4.0 hours (range 1.5–12.0) for Mopral®. C_{max} with Ompranyt® occurred 0.5 hours earlier than with Mopral®, but the difference was not statistically significant (z = −0.4110, p = 0.6811).

Formulation and treatment sequence effects were statistically evaluated by means of ANOVA. In the fasting condition, no significant effect was found on C_{max} for either formulation or treatment sequence factors (p = 0.9239 and p = 0.8827, respectively). With respect to $AUC_{0\text{-}12}$, no significant effect was found for the formulation factor (p = 0.2706), but a significant effect (p = 0.0111) appeared when the treatment sequence factor was considered. In the presence of food, no significant effect was found for formulation or treatment sequence factors on either C_{max} (p = 0.2476 and p = 0.6661, respectively) or on $AUC_{0\text{-}12}$ (p = 0.2794 and p = 0.1962, respectively).

The omeprazole pharmacokinetic parameters obtained in fed and in fasting conditions with each formulation were compared (fed/fasting). With Ompranyt®, the PE was 0.40 (90% CI 0.33, 0.49) for C_{max} and 0.66 (90% CI 0.57, 0.75) for $AUC_{0\text{-}12}$; C_{max} occurred 1.5 hours later in the presence of food than under fasting conditions (z = 4.4472, p < 0.0001). With Mopral®, the PE was 0.34 (90% CI 0.26, 0.42) for C_{max} and 0.62 (90% CI 0.48, 0.79) for $AUC_{0\text{-}12}$; C_{max} occurred 3 hours later in the fed than in the fasting condition (z = 5.1224, p < 0.0001).

Table II. Point estimate (PE) and 90% CI for the comparison of maximum observed plasma drug concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) from time zero to the last sampling time, at 12 hours (AUC_{0-12}) following administration of Ompranyt® (test formulation) and Mopral® (reference) in fasting and fed conditions (n = 23)

Variable	Fasting		Fed	
	C_{max}	AUC_{0-12}	C_{max}	AUC_{0-12}
PE	1.01	1.09	1.21	1.16
90% CI	0.88, 1.16	0.95, 1.25	0.92, 1.59	0.92, 1.47

Bioequivalence Assessment

Bioequivalence of these two formulations when administered in the fasting condition was accepted based on the two one-sided ANOVA for AUC_{0-12} as well as for C_{max} (table II), because in both cases the 90% CI lay within the acceptance range of 0.80, 1.25. In the presence of food, the bioequivalence criterion was not fulfilled because the upper limit of the 90% CI was above the upper limit of the acceptance range (1.25) for both the AUC_{0-12} and C_{max} ratios.

Compared with fasting, there was a significant reduction in rate (C_{max}) and extent (AUC_{0-12}) of systemic exposure when test and reference formulations were administered with food. The food effect on the pharmacokinetic profile of omeprazole was more marked with Mopral® than with Ompranyt®: 63% and 58% decrease in C_{max} and 38% and 35% decrease in AUC_{0-12}, respectively.

Tolerability

Both products were similarly well tolerated. All adverse events were primarily transient in duration, of mild to moderate intensity, and resolved without any sequelae or need for drug treatment. No subject was prematurely withdrawn from the study as a result of an adverse event.

Discussion

In general, single-dose studies would suffice for the purpose of assessing the relative bioavailability and bioequivalence of two formulations.[3,8] According to the FDA,[3] single-dose studies are considered to be more sensitive for addressing the primary question of bioequivalence (i.e. release of drug substance from the drug product into the systemic circulation) and thus multiple-dose studies are generally not recommended, even in instances where nonlinear pharmacokinetics are present. However, the EMEA considers that there are situations in which steady-state studies may be recommended, as in the case of drugs with time-dependent pharmacokinetics.[8] As mentioned in the introduction to this article, the pharmacokinetics of omeprazole are influenced by the drug's pharmacodynamic effect (on gastric acid suppression), and it may be hypothesised that two formulations with similar bioavailabilities after single doses (still in the presence of low gastric pH) may have different bioavailabilities with repeated dosing (i.e. following an increase in pH). Therefore, in the case of omeprazole, testing after multiple administration may provide a more sensitive assessment of bioequivalence.[15]

Inhibition of gastric acid secretion by omeprazole increases with continuous drug administration and reaches a plateau after about 4 days of therapy.[19] In the present study, the relative bioavailabilities of the two study formulations were assessed following 7 days of administration of each product, which seemed to be sufficient for reaching the plateau of gastric acid secretion inhibition.

According to the prescribing information for omeprazole,[19] patients should be advised to take omeprazole formulations before eating. Therefore, one could argue that there is no need for a bioequivalence study under fed conditions because the product is not intended to be taken after meals. However, both the FDA and the EMEA require that, in addition to a bioequivalence study under fasting conditions, a bioequivalence study under fed conditions be undertaken for all orally administered modified-release drug products.[4,5] Bioequivalence food-effect studies aim to demonstrate comparable bioavailabilities between test and reference products when co-administered with meals.

In the present study, in part 1 (fasting condition trial), the 90% CIs of both the mean AUC_{0-12} and C_{max} ratios lay within the acceptance range of 0.80, 1.25. Therefore, under fasting conditions, bioequivalence of Ompranyt® in relation to the reference formulation Mopral® was demonstrated and these results are consistent with those obtained in a previous study by our group.[15] The t_{max} for Ompranyt® occurred 0.5 hours later than that for Mopral®. However, this difference was not statistically significant and, because of the characteristics of the mechanism of action of omeprazole and the formulation type, this difference also cannot be considered to be clinically relevant because, as clearly stated by the EMEA, "statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects".[8]

In part 2 (fed conditions trial), the mean AUC_{0-12} ratio was 1.16 with a 90% CI of 0.92, 1.47, and the mean C_{max} ratio was 1.21 with a 90% CI of 0.92, 1.59. The upper limit of the 90% CI was beyond the acceptance range of 0.80, 1.25 and, as a consequence, the formulations could not be considered equivalent when administered in the presence of food.

Compared with the fasting condition, the pharmacokinetic profile for both formulations was significantly modified in the presence of food, both with respect to the rate (as assessed by C_{max}) and extent of systemic exposure (as expressed by AUC). These results are different from those obtained by Rohss et al.[20] and Andersson et al.,[6] who reported that food delayed the absorption of omeprazole but did not affect the total amount absorbed. Stedman and Barclay[21] observed the same trend in their review of the pharmacokinetics of PPIs; these authors considered that the food effect on absorption of omeprazole is minimal. Our study complies with the draft recommendations issued by the FDA regarding the study design of food-effect bioavailability and fed bioequivalence studies, which are thought to maximise the effect of food on the bioavailability of a drug substance,[4] and with the guidelines issued by the EMEA.[8] Differences between our results and those reported by the above-mentioned authors may relate to different standardisations of study conditions.

Conclusion

The bioequivalence of Ompranyt® (test formulation) and Mopral® (reference) was demonstrated after repeated dosing in the fasting condition. When both formulations were administered in the presence of a high-calorie and high-fat meal, there was a significant reduction in rate (C_{max}) and extent (AUC) of systemic exposure for both formulations when these parameters were compared with those observed in the fasting condition. The food effect was more pronounced for Mopral® than for Ompranyt®, and the formal bioequivalence criteria between test and reference formulations were not fulfilled in the fed condition.

This study confirmed that omeprazole bioavailability is significantly impaired by the presence of food and, therefore, patients should be advised to take omeprazole before eating.

Acknowledgements

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