Relative Bioavailability of Two Formulations of the Same Proton Pump Inhibitor And High Point Estimates Achieved with Drugs Known to Exhibit High Interindividual Variances

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ABSTRACT

A high interindividual variability of pharmacokinetic parameters is often associated with the properties of many therapeutic drugs and may create a major problem in the assessment of bioavailability. Therefore, appropriate measures should be taken to reduce this kind of effects to lowest possible minimum.

Like other compounds of this drug class, the proton pump inhibitor omeprazole is one of those drug compounds that exhibit high interindividual variability in pharmacokinetic parameters. Therefore, this paper describes a collection of prerequisites and during-study standardizations that successfully keep variability at a minimum. These include the exclusion of slow metabolizers by genotyping, the saturation of the proton pump by multiple dosing, and a close supervision and monitoring of subjects.

Thirtytwo subjects participated in a clinical bioavailability study using a randomized crossover design in order to examine the bioequivalence of two 20 mg omeprazole formulations under fasting conditions. In addition, both drugs were administered with a standard high-fat FDA (Food and Drug Administration) breakfast at the end of the study in order to assess the effect of food on bioavailability.

Both omeprazole products were shown to be bioequivalent under fasting conditions. The point estimate for the Area Under the Plasma Concentration versus Time Curve (extrapolated from zero to infinity, AUC_{0-inf}) ratio (test/reference) was 98.4% with a 90% confidence interval of 84.9% to 114.1%. For the Maximal Plasma Concentration (C_{max}) ratio, the point estimate was 92.5% with a 90% confidence interval of 80.0 to 107.0%. The relatively narrow confidence intervals which remained well within the accepted range of 80-125% support the strict standardization in the study conduct which minimized variability. Food reduced the rate and extent of bioavailability of both formulations whereas the magnitude of food effect was similar for both drugs.

• ***Key words:*** *Omeprazole, bioavailability, point estimate, standardization.* **Nobel Med 2006; 2 (2): 15-21**

ÖZET

AYNI PROTON POMPASI İNHİBİTÖRÜNÜ İÇEREN İKİ FORMÜLASYONUN GÖRECELİ BİYOYARARLANIMI VE YÜKSEK BİREYLERARASI DEĞİŞKENLİK GÖSTERDİĞİ BİLİNEN İLAÇLARLA ULAŞILAN TEPE NOKTA DEĞERLERİ

Farmakokinetik parametrelerin bireylerarası yüksek değişkenlik göstermesi genellikle ilaçların özellikleri ile ilgilidir ve biyoyararlanımlarının değerlendirilmesinde büyük sorunlara yol açabilir. Bu yüzden bu tür etkileri en aza indirecek uygun önlemler alınmalıdır.

Sınıfındaki diğer bileşikler gibi bir proton pompası inhibitörü olan omeprazol de farmakokinetik parametreler açısından bireylerarası yüksek değişkenlik gösterir. Bu nedenle, bu yayın değişkenliği en aza indirmek için gerekli olan çalışma öncesi koşulları ve çalışma sırasındaki standartları tanımlamaktadır. Bu standartlar, genotipleme çalışması ile yavaş metabolize eden bireylerin çalışma dışında bırakılması, çoklu dozlama ile proton pompasının doygunluğa ulaştırılması ve deneklerin yakından denetimi ve gözetimini içerir.

Otuz iki deneğin katıldığı bu klinik biyoyararlanım çalışmasında, 20 mg omeprazol içeren iki ayrı formülasyonun biyoeşdeğerliği, açlık koşullarında randomize çapraz tasarım ile araştırılmıştır. Ayrıca gıdanın biyoyararlanım üzerindeki etkisini değerlendirmek amacıyla her iki ilaç standart yüksek yağ içeren FDA (Food and Drug Administration) kahvaltısı ile verilmiştir.

Omeprazol içeren iki ürünün açlık koşullarında biyoeşdeğer olduğu gösterilmiştir. $AUC_{0\text{-}inf}$ için %90 güven aralığı %84,9 ile %114,1 olup, nokta değeri (test/referans) %98,4 hesaplanmıştır. C_{max} oranı için, %90 güven aralığı %80 ile %107 arasında olup, nokta değeri %92,5'dir. %80 - %125 kabul sınırları içinde bulunan ve nisbeten dar güven aralıklarında ulaşılan sonuçlar, bu çalışmada, değişkenliği en aza indirmek için uygulanan katı standardizasyonun gerekliliğini desteklemektedir. Gıda alımının etkisi, miktar olarak her iki formülasyonda aynıyken; biyoyararlanımın hızını ve oranını azaltmıştır.

• **Anahtar Kelimeler:** Omeprazol, biyoyararlanım, nokta değeri, standardizasyon. **Nobel Med 2006; 2 (2): 15-21**

INTRODUCTION

The proton pump inhibitors such as omeprazole have set a new standard for speed and effectiveness in the first-line treatment of many acid-related gastrointestinal disorders compared to other available therapies.[1-3] Omeprazole is therapeutically used in gastric disorders including duodenal ulcer, ulcus ventriculi, gastrooesophageal reflux disease (GORD), as well as in long-term treatment of pathological hypersecretory conditions such as Zollinger-Ellison syndrome. The safety profile of omeprazole has been well defined after many years of experience [4-7] and has led to an FDA (Food and Drug Administration) approval as a non-prescription drug in the United States for all of the above indications.

Proton pump inhibitors such as omeprazole and other compounds of this drug class are well known to display a large interindividual variance in their pharmacokinetics, particularly with regard to the Area Under the Plasma Concentration versus Time Curve (AUC) and C_{max}, probably also due to different disposition kinetics and metabolism.[8,9] Therefore, the present paper critically appraises the pharmacokinetic properties of the originator and a generic omeprazole as revealed after conducting a clinical bio-availability study under optimally controlled conditions in order to minimize as many factors as possible that could have an influence on variability.

Considerable interindividual variability in the kinetics of omeprazole may partly be attributed to pharmacogenetic differences. There is strong evidence that the AUC of omeprazole is heavily dependent on the genotype for the cytochrome P450 enzyme CYP2C19, the principal determinant for omeprazole elimination. An ethnic variability in the absorption or metabolism of omeprazole has been observed in Asian subjects compared to Caucasians[9] related to the fact that approximately 95% of a Caucasian population but only 80% of an oriental population is considered to be extensive metabolizers of omeprazole.[10] Patients with mutated alleles for CYP2C19 (approximately 5% of a Caucasian population) are profound outliers with respect to the pharmacokinetic properties of omeprazole with as much as three to eight times the AUC for any given dose. Therefore, subjects enrolled in bioequivalence studies with omeprazole have been genotyped as described by A. S. Aynacioglu et al.[11] and only subjects with the extensive metabolizer genotype included in the study in order to minimize variability →

in key parameters such as AUC and C_{max}.

The half-life ($T_{1/2}$) of omeprazole is very short in extensive metabolizers (mean $T_{1/2}$: 0.6 hours) so that there is no measurable concentration of the drug substance in the plasma at 24 hours after dosing and no carry over effects beyond this time.[12,13] In extensive metabolizers, plasma concentrations fall below 5 ng/ml within 12 hours, i.e. below the limit of quantification as has also been described elsewhere.[10,13] Because of the short half-life, a washout period of longer than 24 hours is not required.[14,15]

Chronic treatment with omeprazole causes changes in the AUC of this drug over time.[4,5] Various authors observed a substantial increase in AUC by the administration of the same dose at 24 hour intervals for 4 to 7 days.[12,13,15-17] However, AUC increased only during the first 4 days of treatment. No further increase has been observed during continued treatment.[18] Also, the inhibitory effect of omeprazole on acid secretion increases with repeated once daily dosing, reaches a plateau after 4 days,[19] and decreases gradually on drug discontinuation over 3 to 5 days.

A saturable first pass hepatic metabolism has been proposed as an explanation for this effect.[5] In addition, since omeprazole is rather acid labile and chronic treatment substantially increases gastric pH, the increase in AUC may in part result from the decreased degradation of drug in the stomach because of its enteric coating, associated with the much higher gastric pH attained after several days of treatment.[6,20,21]

Irrespective of the underlying mechanism, there is evidence that AUC and C_{max} substantially increase after chronic dosing [6,21] which resembles typical therapeutic conditions (the usual administration time is at least 2 weeks).

MATERIAL AND METHODS

Omeprazole is a substituted benzimidazole, INN: Omeprazole (IUPAC-name: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridinyl) methyl] sulfinyl] 1*H*-benzimidazole) and constitutes the active ingredient of both the originator Mopral® (AstraZeneca, France, batch no: EG5370) and the generic Omeprazid® (Nobel İlaç, Turkey, batch no: 3K007) 20 mg capsule formulation. Since omeprazole is acid-labile, slow-release micropellet capsules contain an enteric-coated granule formulation ensuring that the active drug is only released after stomach passage. Chemical-pharmaceutical investigations along with a variety of analytical test programs demonstrate that the generic 20 mg entirely correspond to the originator's 20 mg capsules.[22] The active ingredient of Omeprazid® corresponds to the overall quality standards as set forth by granting a Certificate of Suitability. Omeprazid® has been demonstrated to be stable over a time period of at least 36 months. During its shelf life, the product maintains its identity, strength, purity and quality. Both drug products used in this study are considered pharmaceutically equivalent due to comparable analytical test results such as stability and disintegration time, gastric acid resistance, dissolution profiles, as well as chromatographical and microbiological purity patterns.[22]

An open, comparative, randomised, 2-way crossover bioavailability study was performed under fasting conditions in 32 healthy, non-smoking male volunteers aged 18 to 45 years after having obtained written informed consent and Ethics Review Committee approval. A total of 40 subjects were genotyped prior to entry and only those with the extensive metabolizer genotype were included in the study. This was followed by a study on the interaction of food on pharmacokinetic parameters of both test and reference drug.

After pre-study screening and CYP2C19 genotyping, each subject was hospitalized for a total of 9 days to undergo well controlled study conditions. In the morning of study day 1 through to day 5, after an overnight fast, subjects swallowed on an empty stomach one capsule of the investigational drug. Subjects were randomly assigned to the two treatments: Treatment A, (generic test product) and Treatment B, (originator reference product). On study days 6 to 8, each subject received under the same conditions the other study medication following the cross-over design.

Both products containing enteric coated micropellets clearly represent a modified drug release formula. Therefore, it was essential to investigate a potential food effect and to demonstrate that both test and reference drug behave in a comparable manner when administered with food. Therefore, the effect of food on the bioavailability of both formulations was tested on the last day of this study (day 9) with subjects receiving a standardized high fat FDA breakfast of 30 minutes duration prior to drug administration .

A multiple dose design was used for this study since the variability in omeprazole concentrations is reduced as a result of saturation of the H^+-K^+- ATPase system with an increase of gastric pH. Moreover, higher drug plasma concentrations that result from multiple dosing allow a more accurate AUC determination.

During the course of the study, subjects were required to remain in the intensive care unit for a total of nine days ensuring strict compliance with key protocol para- →

meters: no other medications with the sole exception of treating adverse events were allowed and alcohol was prohibited throughout the study and for 3 days prior to study. Subjects were allowed to drink water *ad libitum* except for one hour before and after drug intake. There was no special diet on the day prior to study start.

A total of eight nurses/physicians were available throughout the study in order to ensure that there were a maximum of 4 subjects per nurse or study physician throughout the blood sampling period. Subjects were kept under observation in order to ensure that they maintained a sitting position at drug intake and for at least three hours thereafter. No standing, lying or walking was permitted during this time period.

Pharmacokinetic blood sampling was done on study days 5, 8 and 9 exactly at the following time intervals (no time window allowed): At 0 (pre-dosing), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.75, 5.25, 6.0, 8.0, 10.0, 12.0, 16.0, and at 23.5 hours post drug administration. In addition, pre-dose blood samples were drawn on study days 1, 2, 3, 4, and 7. Blood samples were obtained by venipuncture and placing an indwelling catheter in the subject's arm. Five ml of blood were collected into EDTA Vacutainer® tubes (pale violet) and cooled on ice until centrifugation at 2000 x g for 20 minutes at 4°C. Plasma was transferred into labeled stoppered polypropylene tubes avoiding carry-over of erythrocytes. In order to stabilize omeprazole in the plasma, 10 µl of 1M sodium carbonate solution was added per 2.5 ml of plasma. Samples were immediately stored at –20°C.

Omeprazole concentrations were determined by HPLC employing reversed phase chromatography on Nucleodur C-18ec (5 µm) with isocratic elution and UV detection at 302 nm (using a solid phase extraction to isolate omeprazole from plasma). The mobile phase consisted of a phosphate buffer (pH 8.1) -acetonitrile mixture. Quantification was accomplished by means of the internal standard procedure, calibration was done by calculating weighted (l/y) linear regression from peak height ratios versus nominal concentrations. The limit of quantification was determined to be 5 ng/mL (lowest calibrator) as determined during pre-study validation. The precision of the assay, as determined from the analysis of quality control samples, was within 5% of nominal values at all concentrations. Calibration curves were prepared daily over a concentration range from 5 to 1000 ng/mL. Accuracy of the assay was within ± 5% of the nominal value for all quality control samples.

Primary parameters included adverse events for drug safety, $AUC_{0\text{-}inf}$ and C_{max} for bioequivalence. The time to maximum plasma concentration (T_{max}), and half-life ($T_{1/2}$) for omeprazole were considered as secondary parameters. C_{max} and T_{max} were obtained directly from the plasma concentration- time curve for each subject. The elimination rate constant (k) was obtained from the slope of a plot of natural logarithm of concentration vs. time. Only concentrations that were clearly postabsorption were used to estimate k. The half-life ($T_{1/2}$) was calculated as 0.693/k. The area under the plasma concentration-time curve from 0 to the last quantifiable concentration ($AUC_{0\text{-}t}$) was calculated using the linear trapezoidal rule. The area under the plasma concentration time curve from 0 to infinity ($AUC_{0\text{-}inf}$) was calculated according to the following formula:

$$AUC_{0\text{-}inf} = AUC_{0\text{-}t} + \frac{Ct}{k}$$, with Ct being the lowest quantifiable plasma concentration.

The log-transformed $AUC_{0\text{-}inf}$ and C_{max} for each subject with both treatments were used to calculate the ratio of the test (Treatment A) and reference formulation (Treatment B). A standard bioequivalence data analysis was done based on the two one-sided t-test procedure for the log-transformed C_{max} and $AUC_{0\text{-}inf}$ values (90% confidence interval approach). The bioequivalence limits for $AUC_{0\text{-}inf}$ were set to 80 and 125%, those for C_{max} to 70 and 143% of the reference formulation. The paired t-test was used to assess the effect of food on the C_{max}, $AUC_{0\text{-}inf}$ and T_{max} for both formulations. The statistical analysis of the data was carried out using the computer program SYSTAT for Windows, Version 5 (SYSTAT Inc., Evanston, IL, USA).

RESULTS

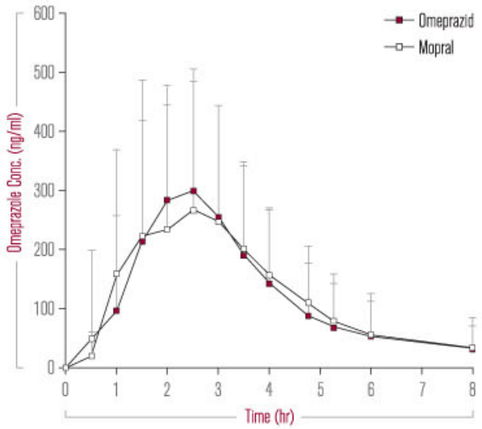
A comprehensive overview of the results obtained for key pharmacokinetic parameters are presented in Table 1.

Table 1: Mean values for primary pharmacokinetic parameters

PARAMETER	GENERIC (Test)	ORIGINATOR (Reference)	T/R Ratio[1]	90% CONFIDENCE LIMITS	
				Lower	Upper
$AUC_{0\text{-}inf}$ (ng*hr/mL)	884.7	892.4	98.4	84.9	114.1
C_{max} (ng/mL)	392.5	420.6	92.5	80.0	107.0
T_{max} (h)	2.22	2.48	-	-	-
k (h^{-1})	0.77	0.78	-	-	-
$T_{1/2}$ (h)	1.01	0.98	-	-	-

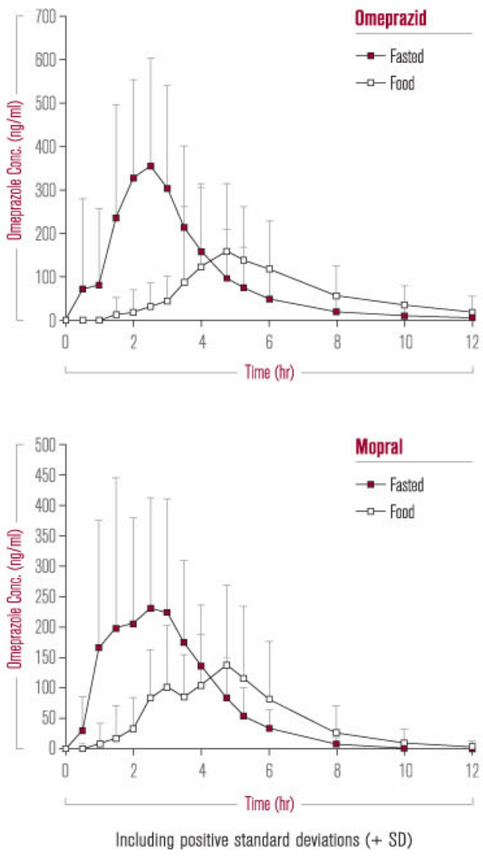
[1] Log-transformed ratio of Test/Reference x 100. **$AUC_{0\text{-}inf}$:** Area Under the Plasma Concentration versus Time Curve extrapolated from zero to infinity; **C_1:** Maximal concentration in the plasma; **T_{max}:** Time to reach maximal plasma concentration; **k:** Elimination rate constant; **$T_{1/2}$:** Terminal half life

After administration of both formulations, plasma levels of omeprazole started to rise in most subjects after 0.5 h and reached peak values between 2 and 3 hours. In 29 out of 32 subjects, they declined to undetectable levels within 12 hours; in all subjects within 24 hours. The interindividual variability (CV) for pharmacokinetic key parameters was low for omeprazole. The CV for $AUC_{0\text{-}inf}$ was 34.64% and 34.50% for C_{max}. Although the interindividual variability in omeprazole kinetics are known to be high, the mean plasma levels during the 24 hour period after administration of the test and reference products were quite similar (see Figure 1). Since both, test and reference formulations display quite a similar plasma concentration profile, it was not surprising that the mean values for the primary pharmacokinetic parameters were similar as well. Therefore, the bio-availability of the reference (R) and test (T) product was compared by using the ratios of their log-transformed $AUC_{0\text{-}t}$ values by using the following data:



Including positive standard deviations (+ SD)

Figure 1. Mean plasma concentrations of omeprazole after administration of the generic and originator product under fasting conditions.



Including positive standard deviations (+ SD)

Figure 2. Mean plasma concentrations of omeprazole after administration of the generic and originator product under fasting conditions and with food.

Treatment A: Reference (R) for the initial 5 days (analysis at day 5) = R 5d; Test (T) for the subsequent 3 days (analysis at day 8) = T 3d.

Treatment B: Test (T) for the initial 5 days (analysis at day 5) = T 5d; Reference (R) for the subsequent 3 days (analysis at day 8) = R 3d.

The terms R_F and T_F indicate groups of subjects with additional food intake.

In addition to the comparison of all reference and test product values, an analysis of the sub-groups was performed as well in order to demonstrate any potential time-dependent changes in the absorption of omeprazole which might have affected either $AUC_{0\text{-}inf}$ or C_{max}.

Table 2: Impact of Time on the absorption of omeprazole (fasting conditions)

	$AUC_{0\text{-}inf}$ RATIO		C_{max} RATIO	
	Mean[1]	Range[2]	Mean[1]	Range[3]
T 5d/R 5d	95.6	90.6 - 100.6	92.4	87.4 - 97.4
T 5d/R 3d	101.3	98.3 - 104.3	99.1	95.1 - 103.1
T 3d/R 5d	99.1	96.1 - 102.1	99.2	95.2 - 103.2
T 3d/R 3d	107.5	97.5 - 117.5	109.1	98.1 - 129.1
T 5+3d/R 5+3d	100.2	97.2 - 103.2	99.1	95.1 - 103.1

[1] Ratios of ln-transformed values x 100; [2] Accepted range 80 -125%; [3] Accepted range 70 -143%; **T:** Test drug; **R:** Reference drug; **$AUC_{0\text{-}inf}$:** Area Under the Plasma Concentration versus Time Curve extrapolated from zero to infinity; **C_1:** Maximal concentration in the plasma

As shown in Table 2, all calculated ratios of $AUC_{0\text{-}t}$ and C_{max} values are within the acceptable range without any difference between the test and reference formulation. All calculated data were within the acceptable range. Comparing $AUC_{0\text{-}inf}$ and C_{max}, these values correspond well to those published by Sohn et al.[9]

As shown in Figure 2, the intake of food decreased the →

C_{max} values measured after application of both formulations. The use of the Analysis of Variance (ANOVA) as well as the determination of the ratios of the log-transformed values showed that food intake significantly reduced the C_{max} values within the same formulation. Figure 2 also indicates that a similar effect was observed for the reference as well as for the test product. When using paired values, the mean decrease in C_{max} was 46.7% for the reference and 52.1% for the test formulation.

T_{max} was significantly delayed ($p<0.05$) for both formulations after food intake which decreased AUC_{0-t} of the reference from 1013.5 to 791.2 ng*hr/mL (the mean decrease of the paired values was 16.6%, p=0.09). The concomitant application of food and the test product decreased AUC_{0-t} from 791.9 to 594.4 ng*hr/mL (mean decrease of the paired values was 21.0%, $p<0.05$).

Table 3 summarizes these results and supports a comparable decrease in pharmacokinetic parameters for both formulations indicating that both formulations were affected in a similar way by food.

Table 3: Comparable impact of food on the absorption of test and reference drug

	C_{max} (ng/mL)		AUC_{0-inf} (ng*hr/mL)	
	Mean	**CI (95%)**	**Mean**	**CI (95%)**
T 3d	479	129.0	1013.5	496.4
T_F 3d	197	84.0	791.2	387.7
R 3d	375	110.7	791.9	388.0
R_F 3d	176	64.0	594.5	291.2

	C_{max} RATIO		AUC_{0-inf} RATIO	
	Mean[1]	**Range[2]**	**Mean[1]**	**Range[3]**
T_F 3d/R_F 3d	113.5	66.8 - 160.2	106.6	94.6 - 118.6
T_F 3d/T 3d	83.1	48.9 - 117.3	94.2	89.2 - 98.8
R_F 3d/R 3d	32.3	19 - 45.4	95.3	92.5 - 98.1

[1] Ratios of ln-transformed values x100; [2] Accepted range 70–143%; [3] Accepted range 80–125%; **T:** Test drug (fasting); **T_F:** Test drug (fed); **R:** Reference drug (fasting); **R_F:** Reference drug (fed); **AUC_{0-inf}:** Area Under the Plasma Concentration versus Time Curve extrapolated from zero to infinity; **C_1:** Maximal concentration in the plasma

DISCUSSION

The results of this study indicate that the pharmacokinetic properties of omeprazole are almost exactly the same following an administration of either the generic or the originator product. The point estimate of close to 100% for the AUC ratio along with the relatively narrow confidence intervals that lie within the generally accepted range of 80-125% not only leads to the conclusion that these products are bioequivalent, but the almost identical bioavailability profile of the generic and the originator product also indicates that the high-quality generic formulation exhibits a therapeutic potential considerably comparable with the originator. Moreover, a significantly reduced interindividual variability (CV) for key pharmacokinetic parameters such as AUC_{0-inf} (34.64) and C_{max} (34.50) can only be achieved with this drug class by a strict standardization of as many study conditions as possible. Importantly, such results are considered achievable only by adhering particularly to the following conditions:

- Hospitalization of subjects during the entire course of the study which prevents uncontrolled events such as additional food intake that may have an influence on study results.
- Close monitoring of subjects to ensure the same prerequisites at drug intake and during drug absorption.
- Genotyping of subjects in order to detect and exclude slow metabolizers.
- Using a multiple dose regimen which saturates the H^+-K^+- ATPase proton pump.

In detail, the results of this study indicate that the generic formulation is bioequivalent to the originator when both products are administered under fasting conditions. The 90% confidence interval for the AUC_{0-inf} ratio (test/reference) was 84.9-114.1% with a point estimate of 98.4%. In addition, both the point estimate (92.5%) and the 90% confidence interval (80.0-107.0%) for the C_{max} ratio are within the predetermined limits of 70-143% although the C_{max} ratio is known to constitute an inherently more variable parameter than AUC. In addition, since there was no detectable omeprazole in any sample collected 24 hours after dosing, the clear absence of any carry-over effect between treatments could be well documented.

Food appears to slow down and reduce the absorption of both products to a similar extent. C_{max} was lower for both products when given with food and T_{max} was significantly prolonged. AUC_{0-t} was reduced as well by food but to a less pronounced extent than C_{max}. Although the magnitude of the effect of food on AUC_{0-inf} was similar for both products (mean decrease of 16.6% with the generic versus 21.0% with the originator), the difference was statistically significant only with the originator.

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