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Comparative pharmacokinetic analysis with Two Omeprazole Formulations "Proceptin®" and "Losec®" in Healthy Subjects

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ABSTRACT

The pharmacokinetics of omeprazole pharmaceutical products Proceptin® 20mg capsule and Losec® 20mg MUPS tablet were compared in healthy subjects. The study was an open-label, randomized, two-treatment, two-sequence, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of seven days between the two administrations. Blood samples were collected pre-dosing and at 0.5–24.0 h post administration of a single oral dose of either of the formulation followed by HPLC analysis. Twenty-eight healthy male subjects (20-28 years) participated in the study. Only four subjects dropped from the study and the other 24 completed the study and were included in the pharmacokinetic and statistical analysis. Evaluated mean (±SD) values of prime pharmacokinetic parameters for reference and test products were C_{max} - 345.28 (±42.38) and 316.23 (±26.12) ng/mL, t_{max} - 2.28 (±0.16) and 2.69 (±0.23) h, AUC_{0-24} - 710.01 (±92.51) and 771.13 (±102.35) h-ng/ml and $AUC_{0-\infty}$ - 848.21 (±65.31) and 902.56 (±45.23) h.ng/mL, respectively with no significant (p>0.05) differences in paired t-test. Moreover, 90% CI for the AUC_{0-24}, and C_{max} values were 89.245-103.154% and 81.634-102.211% respectively were within the predetermined FDA bioequivalence range of 80–125%. On the basis of the pharmacokinetic parameters AUC_{0-24}, the relative bioavailability of the test preparation Proceptin 20 capsule was 108.61% of that of the reference preparation Losec 20mg MUPS tablet. This study stipulated that, the test and reference formulations of omeprazole meet the regulatory criteria for bioequivalence. Thus the test product Proceptin® 20mg may be supplanted for reference product Losec® 20mg MUPS tablet in oral administration.

KEY WORDS: ***Omeprazole; Cross-over design; HPLC; Comparative pharmacokinetics***

INTRODUCTION

Omeprazole, a substituted benzimidazole, is one of the most widely prescribed drugs internationally and over the counter drug in some countries. As a pro-drug after conversion to its active form in the parietal cell it binds irreversibly[1] (**Figure 1**)

with H^+/K^+-ATPase (the gastric proton pump), which causes an effective and long-lasting inhibition of gastric acid secretion[2-4]. Therefore, omeprazole is widely used in the treatment of active duodenal ulcer, gastro-esophageal reflux disease (GERD), erosive esophagitis, active benign gastric ulcer, Zollinger-Ellison syndrome, infection of *Helicobacter pylori* as part of combination regimens and or other pathological hypersecretory conditions[5-6].

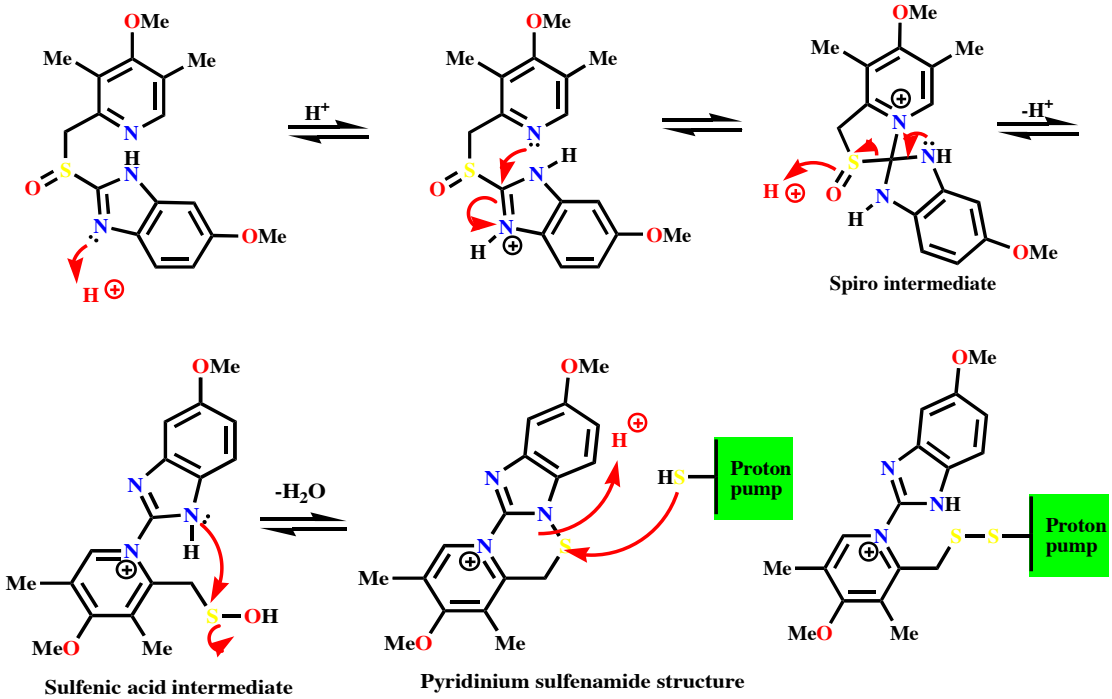

Figure 1: The proton pump inhibitor, omeprazole as pro-drug is converted to its active form in acidic medium. As weak base it specially concentrates in the acidic secretory canaliculi of the parietal cell, where it is activated by a proton-catalyzed process to generate a sulfenamide intermediate. The sulfenamide interacts covalently with sulphydryl groups of cysteine residues in the extracellular domain of the proton pump (H^+K^+-ATPase) there by inhibiting its activity[1].

From a pharmacokinetics perspective, omeprazole is absorbed rapidly, and systemic availability in humans is approximately 60% after an oral dose of a 40 mg capsule, which indicates a fairly extensive first-pass metabolism[7]. The protein binding of omeprazole in human plasma is about 95%[8-9]. It is metabolized into 5-hydroxyomeprazole and omeprazole sulfone by CYP2C19 and CYP3A4, respectively and the overall metabolism of it depends more on the activity of CYP2C19 than that of CYP3A4[10-12]. The 5-hydroxyomeprazole is more than 100 times less potent than omeprazole, and the omeprazole-sulphone does not possess any antisecretory activity[8]. Omeprazole is eliminated by metabolism with a mean plasma $t_{1/2} \leq 1.0$ h. In healthy individuals, about 80% of a given dose is excreted as metabolites in the urine and about 20% in the feces[7-9].

The multi unit pellet system (MUPS) tablet is a patented formulation of omeprazole designed to optimize delivery of omeprazole to the site of its absorption in the small intestine. In particular, the gastro-resistant properties of the multiple layered

micropellets are important to protect the acid-labile omeprazole from gastric juices. Since omeprazole is not stable at acidic pH, enteric-coated formulations are administered and therefore, wide variability in the absorption of formulations of this drug may exist owing to differences in coating which may influence protection against the acid and, consequently, may affect bioavailability[13,14]. Enteric-coated formulations of omeprazole reached mean maximal concentration ranging from 400 to 800ng/ml[15-19] demonstrating its wide pharmacokinetic variability.

Hence, the purpose of this study was to determine the various pharmacokinetic parameters such as maximum plasma concentration (C_{max}) at the time (t_{max}), area under the plasma concentration time curve (AUC_{0-t}), area under plasma concentration time curve up to infinity ($AUC_{0-\infty}$), plasma elimination rate constant (k_{el}), the plasma elimination half life ($t_{1/2}$) after oral administrations of omeprazole enteric coated pellet formulations Proceptin® 20mg capsule and Losec® 20mg MUPS tablet.

METHODOLOGY

Drugs and reagents

Two commercially available brands of 20 mg omeprazole, Proceptin® capsule (test preparation); Batch No: SUL067, DAR No: 186-98-34 manufactured by Beximco Pharmaceutical Ltd. Dhaka, Bangladesh and Losec® 20mg MUPS tablet (reference formulation); Batch No: MK11085 manufactured by Astra Zeneca, Sweden containing omeprazole magnesium. Omeprazole (98.97% purity), used for the preparation of Proceptin® capsule were collected from the manufacturer for analysis and method development; and pantoprazole (96.98% of purity), used as an internal standard were purchased from Reddy's Laboratories Ltd. (Hyderabad, India). Deionized water was prepared using Milli-Q system (Continental Water Systems, El Paso, TX, USA). E. Merck (Darmstadt, Federal Republic of Germany) supplied HPLC grade methanol. Other reagents used were of analytical grade.

Subjects

Twenty-eight healthy male Bangladeshi subjects aged 20-28 yr and body mass index ranging from 17.5 to 23.65 kg/m^2 participated in this study. None of the subjects was an alcohol user, drug abuser, concomitant medication user and smoker during the period of the study. Demographic data was collected from all the participants who gave written consent after reading the protocol approved by the clinical review committee, Faculty of Pharmacy, University of Dhaka.

Study design

An open label, randomized, two-way, crossover study was designed. There were two dosing sessions with a 15 d washout period. All the volunteers were required to participate in two dosing sessions with a wash out period of seven days between the two administrations. In each dosing session, volunteers received either the test preparations or reference preparations as a single dose, only on the study day, as per the randomization code at a fixed time. Volunteers were in fasting condition before drug administration. The study preparations were allowed to ingest with 200mL of water. Standard breakfast, lunch, snack and dinner were served at 2, 5, 8 and 12 hours of post-drug administration respectively in each period of the study. Volunteers were given code numbers. They were allocated to the treatment (reference or test preparation) in accordance with the randomization code. Neither the personnel in charge of the determination of plasma levels nor the physician and nursing staff in charge was informed of the sequence of administration.

Ethical review and consent procedure

Guidelines as drawn up by the Bangladesh Medical Research Council (BMRC) were followed with regard to the treatment of human volunteers in the study. These guidelines met the requirements of the U.I S. Code of Federal Regulations (Title 21, Part 56), the Declarations of Helsinki[20] and the Canadian MRC Guidelines. The protocol containing the aims and objectives, and research procedure was submitted for ethical clearance and was approved by BMRC (number: BMRC/NERC/DO 2010-2013/1019 date 05.08.2012). All the participants were informed about the nature and purpose of the study. For assurance of the complete understanding of the protocol, a written consent form was obtained from each participant included in the study.

Blood sampling

An indwelling-intravenous catheter (Vasofix, Germany) was inserted into a suitable forearm vein with strict aseptic precautions for blood sampling. Five ml of blood were withdrawn during each time and were collected by a nurse prior to dosing at 0 min (baseline) and 0.5, 1.0, 2.0, 3.0, 5.0, 8.0, 12.0, and 24.0 h after dosing. Heparinized blood samples were centrifuged for 25 min after collection at 3500 rpm for 20 min at 2-8^{o}C. Plasma was separated and stored at -80°C until analysis.

Sample preparation

One ml of plasma sample was mixed with 100 µl of methanol: acetate buffer (pH 4.6, 1:4 v/v) mixer followed by further mixing with 5.0 ml of dichloromethane: acetonitrile (4:1 v/v). The blend was vortexed for 30 sec. Again, after centrifugation at 4500 rpm for 10 min, 4.0 ml of organic phase separated and evaporated under a nitrogen stream. The residue was dissolved in 200 µL of mobile phase and 100 µL of it was injected into the HPLC chromatographic system.

Chromatographic analysis

Shimadzu Prominence (Kyoto, Japan), an HPLC system that consists of a SCL-20 AVP system controller with two pumps (Kyoto, Japan), determined the omeprazole and internal standard pantoprazole plasma levels. Separation of compounds was carried out by Luna C_{18} column (5µ, 4.6 × 250 mm) (Phenomenex, Torrance, California, USA) eluted with water and acetonitrile (58:42, v/v) at room temperature at a flow rate of 1.0 ml/min. Ultraviolet detection was achieved with SPD-20AVP UV-VIS detector (Shimadzu Corporation; Kyoto, Japan) at 302 nm.

Pharmacokinetic analysis

Plasma drug concentrations at defined time points of the study were used in pharmacokinetic calculations. Pharmacokinetic parameters were derived for both test and reference product. Data set was prepared for the estimation of pharmacokinetic parameters by using program kinetica (version 4.4, Adept Scientific, UK) followed by non-compartmental method of analysis. The pharmacokinetic parameters included were maximum plasma concentration (C_{max}), time to reach the maximum concentration (t_{max}), half-life ($t_{1/2}$), area under the plasma concentration-time curve up to last quantifiable time (AUC_{0-24}), area under the plasma time curve up to time infinity ($AUC_{0-\infty}$), elimination rate constant (k_{el}), mean residence time (MRT), area under the moment curve up to last quantifiable time (AUM_{0-24}), area under the moment curve up to time infinity $AUM_{0-\infty}$, and the ratio $C_{max}/AUC_{0-\infty}$.

Statistical Analysis

Pharmacokinetic data was statistically analyzed by using paired t-test. Comparison of pharmacokinetic parameter C_{max}, AUC_{0-24}, $AUC_{0-\infty}$ and ratio for untransformed and ln-transformed data with respect to test and

reference formulations were analyzed using ANOVA (Dublin, Ireland). This analysis reflected the significance of various effects such as period, sequence, and subject tested within sequence. The predetermined equivalence range of 80-125% and $p \leq 0.05$ for the 90% CIs according to the guidelines of the USFDA were the basis of bioequivalence confirmation.

RESULTS

Under the analytical conditions, the retention time of omeprazole and pantoprazole were 5.44 and 3.67 min respectively. No interfering peaks observed at corresponding retention time. A linear relationship (r^2 = 0.9972) was obtained in the calibration curve constructed over a range of 0.0-200 ng/mL. Coefficient of variation was always lower than 8%. The method had a precision of 96.99 ± 4.89 % and its limit of detection was 5.0 ng/mL.

Pharmacokinetic parameter

Pharmacokinetic parameters calculated from plasma drug level at defined time points for both reference and test products tabulated in **Table 1**.

For reference and test products, the mean (SD) values of pharmacokinetic parameters were C_{max}; 345.28 and 316.23 ng/ml, t_{max}; 2.28 and 2.69 h, $t_{1/2}$; 2.57 and 2.39h AUC_{0-24}; 710.01 and 771.13 h-ng/mL, $AUC_{0-\infty}$; 848.21 and 902.56 h-ng/ml, MRT; 4.25 and 4.38h AUM_{0-24}; 174.51 and 192.56 h^2ng/ml, $AUM_{0-\infty}$; 195.28 and 215.254 h^2ng/ml, and k_{el}; 0.269 and 0.289 respectively. The Least Square Mean (LSM) ratios (%) in 90% CI of the ln-transformed values were 81.634 – 102.211 % for C_{max}, 89.245 – 103.154 % for AUC_{0-24}, and 86.264 – 104.218 % for $AUC_{0-\infty}$ (**Table 2**). On the basis of the pharmacokinetic parameters, the relative bioavailability of the generic test preparation Proceptin 20mg Capsule was 108.61% to that of reference formulation Losec 20mg MUPS Tablet.

Mean plasma-concentration-against-time curves of two oral pharmaceutical formulations: Losec® and Proceptin® showed in **Figure 2** exhibited a similar kinetics.

Inter-individual variability in omeprazole plasma concentrations was small. Subject variation was evidenced at 10 percent significant level for C_{max} ($p<0.01$), AUC_{0-24} ($p<0.01$), $AUC_{0-\infty}$ ($p<0.01$), AUM_{0-24} ($p<0.01$) and $AUM_{0-\infty}$ ($p<0.01$) but no variation regarding formulation, period and sequences aspect are observed (**Table 3)**. For all subjects, there was a very fast absorption with a peak concentration of 345.28 and 316.23 ng/ml being attained at 2.28 and 2.69 h for reference and test formulation respectively. The half-life of the reference and test products was also 2.57 h and 2.39 h respectively. No statistically significant differences observed in pharmacokinetic parameters when both formulations compared by paired *t* test depicted in **Table 4**.

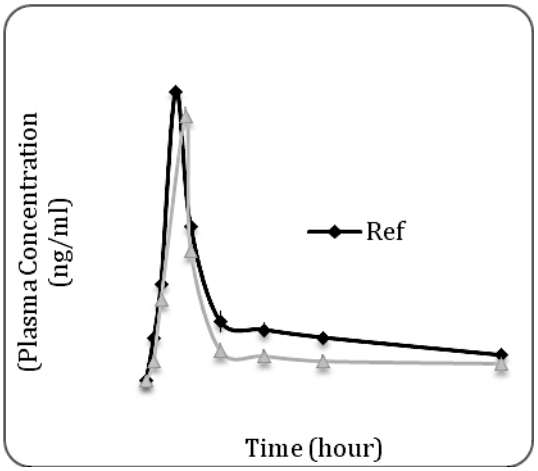

Figure 2. Mean plasma-concentration-time curve of omeprazole after oral administration of two formulations: Reference (Losec®) and Test (Proceptin®) products to healthy subjects.

Table 1: Plasma pharmacokinetic parameters of all the volunteers for test and reference formulations

Pharmacokinetic Parameters	Mean ± SD[a]	Geometric Mean	CV (%)[b]	Max	Min
Reference formulation					
C_{max} (ng/ml)	345.28 ± 42.38	335.46	25.35	378.43	197.54
t_{max} (h)	2.28 ± 0.16	2.19	34.56	2.56	1.9
AUC_{0-24}(h. ng/ml)	710.01 ± 92.51	702.56	43.46	805.58	596.63
$AUC_{0-\infty}$(h.ng/ml)	848.21 ± 65.31	835.23	38.54	942.51	605.74
MRT(h)	4.25 ± 0.342	4.04	23.45	4.83	3.88
$AUMC_{0-24}$ (h^2ng/ml)	174.51 ± 0.04	170.56	35.33	187.44	130.02
$AUMC_{0-\infty}$(h^2ng/ml)	195.28 ± 0.06	189.47	32.67	257.46	134.53
K_{el}	0.269 ± 0.04	0.226	25.46	0.299	0.185
$t_{1/2}$ (h)	2.57 ± 0.53	2.35	26.34	2.99	2.25
$C_{max}/AUC_{0-\infty}$	0.407 ± 0.03	0.387	35.77	0.463	0.346
Test formulation					
C_{max} (ng/ml)	316.23 ± 26.12	310.48	28.46	369.63	185.04
t_{max} (h)	2.69 ± 0.23	2.37	33.54	2.97	1.83
AUC_{0-24}(h. ng/ml)	771.13 ± 102.35	763.42	42.76	825.82	584.33
$AUC_{0-\infty}$(h.ng/ml)	902.56 ± 45.23	897.49	41.35	942.51	605.25
MRT(h)	4.38 ± 0.257	4.24	36.66	5.12	3.57
$AUMC_{0-24}$ (h^2ng/ml)	192.56 ± 0. 02	185.38	40.32	237.65	140.58
$AUMC_{0-\infty}$(h^2ng/ml)	215.25 ±0.13	205.56	43.57	266.49	154.66
K_{el}	0.289 ± 0.08	0.235	29.57	0.332	0.164
$t_{1/2}$ (h)	2.39 ± 0.79	2.14	34.43	3.24	2.16
$C_{max}/AUC_{0-\infty}$	0.350 ± 0.21	0.281	37.66	0.384	0.314

aSD=Standard Deviation; bCV=Coefficient of Variance

Table 2: The 90% confidence Interval with the Test and Reference Preparation

Parameter	Untransformed data	In transformed data
C_{max}	0.88645 – 1.10241%	0.81634 – 1.02211%
AUC_{0-24}	0.86230 – 1.22654%	0.89245 – 1.03154%
$AUC_{0-\infty}$	0.85056 – 1.02598%	0.86264 – 1.04218%

Table 3: The p values for sources of variations obtained from Analysis of Variance (ANOVA)

Pharmacokinetic parameters	Sources of variation			
	Formulation	Period	Sequence	Subject
C_{max} (ng/ml)	0.12	0.77	0.66	0.01
t_{max} (h)	0.77	0.57	0.84	0.06
AUC_{0-24} (h.ng/ml)	0.84	0.78	0.66	0.01
$AUC_{0-\infty}$ (h.ng/ml)	0.64	0.89	0.75	0.01
MRT (h)	0.85	0.56	0.83	0.26
$AUMC_{0-24}$ (h^2ng/ml)	0.96	0.77	0.52	0.01
$AUMC_{0-\infty}$ (h^2ng/ml)	0.93	0.65	0.72	0.01
K_{el}	0.74	0.84	0.61	0.17
$t_{1/2}$ (h)	0.86	0.72	0.84	0.15

Table 4: The p values of paired t-test

Pharmacokinetic parameters	*p* values
C_{max} (ng/ml)	0.257
t_{max} (h)	0.657
AUC_{0-24} (h.ng/ml)	0.879
$AUC_{0-\infty}$ (h.ng/ml)	0.856
MRT (h)	0.763
$AUMC_{0-24}$ (h^2ng/ml)	0.451
$AUMC_{0-\infty}$ (h^2ng/ml)	0.485
K_{el}	0.640
$t_{1/2}$ (h)	0.359

DISCUSSION

Two striking observations regarding high variability between individuals and substantial differences between the two formulations within each individual are the significant consideration in any comparative pharmacokinetics study. Considerable inter-individual variability, particularly in C_{max} AUC and AUM is depicted for both formulations of omeprazole. This variability can be largely attributed to genetic polymorphism of the cytochrome P450 (CYP) isoform CYP2C19[21-23]. Besides age, concomitant medication and differences in weight could add to the high inter-individual variability.

In order to establish if the formulations tested were bioequivalent, pharmacokinetic parameters for both formulations were compared by analysis of variance, and no statistically significant difference was observed. Moreover, ratios and 90% confidence limits for AUC_{0-24} and C_{max} were calculated. Confidence limits 89.54 (81.634 – 102.211%) for C_{max} and 104.34 (89.245 – 103.154%) for $AUC_{0–24}$ were within the limits of acceptance, which justified bioequivalence standard (**Table 2**). These limits of acceptance were selected based on the variability of omeprazole pharmacokinetics and double peaks or major shouldering characteristics[14-18]. It has been proposed that, in case of drugs with a wide variability in absorption, these limits are adequate[24,25] and are currently accepted in Europe.

From the results it was observed that the relative bioavailability of the generic test preparation Proceptin 20mg Capsule is 108.61% equivalent to that of reference formulation Losec 20mg MUPS Tablet. This result confirmed the predetermined equivalence range of 80-125% with $p \leq 0.05$ for the 90% CIs according to the guidelines of the USFDA.

From a comparison perspective, pharmacokinetic parameters of omeprazole obtained in Bengali healthy subjects are not completely in accordance with data reported in the literature. Racial and ethnic variations in drug pharmacokinetics have no exception. As a fact of precedence, Poo *et al*[1] have reported that omeprazole capsules 20 mg orally administered to 34 healthy Mexican volunteers produced mean reference verses test in $AUC_{0–t}$, C_{max}, T_{max}, and $t_{1/2}$ values of 0.88 and 0.92 µg.h/ml, 0.49 and 0.48 µg/ml, 1.9 and 2.0 h, 0.85 and 0.91 h respectively. Allegrini *et al*[26] have found that omeprazole 20 mg capsules in 50 healthy Italian male and female volunteers produced a mean reference verses test preparations of $AUC_{0–t}$ 908.95 and 900.83 ng.h/ml, C_{max} 447.61 and 436.31 ng/ml, T_{max} 2 and 2 h, and $t_{½}$ 1.27 and 1.06 h respectively. Rhim *et al*[27] studied with omeprazole 20 mg administering in healthy Korean male volunteers and reported a mean reference versus test preparation of $AUC_{0–24}$ of 1223.3 and 1284.3 ng.h/ml, C_{max} of 598.7 and 598.1 ng/ml, T_{max} of 1.9 and 1.9 h, and $t_{1/2}$ of 1.3 and 1.4 h respectively.

However, in the present study, mean test versus reference preparations of AUC_{0-24} was 771.13 and 710.01 ng.h/ml, C_{max} was 316.23 and 345.28 ng/ml, T_{max} was 2.69 and 2.28 h, and $t_{1/2}$ was 2.39 and 2.57 h respectively. In this study the lowest C_{max} and comparatively higher T_{max} and $t_{1/2}$ values were observed in Bengali population in comparison to Mexican, Italian and Korean subjects. These differences may be due to especially for CYP2C19 and CYP3A4 genotypes[21-23] and may be due to two different formulations considered in the comparative study. Single dose design and young healthy volunteer selection are main cruxes of limitation of this study as pharmacokinetics in patients may not be similar.

CONCLUSION

The results of the study stipulate that, the test and reference formulations of omeprazole meet the regulatory criteria for bioequivalence but omeprazole pharmacokinetics varies in healthy subjects. On the basis of the pharmacokinetic parameters studied among the two formulations, it can be concluded that the test preparations Proceptin 20mg capsule was bioequivalent to the reference product Losec 20 mg MUPS tablet and can be substituted.

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REFERENCES

1. Lindberg P, Nordberg P, Alminger T, Brändström A, Wallmark B. The mechanism of action of the gastric acid secretion inhibitor omeprazole. *J Med Chem.* 1986;29(8):1327-9.
2. Poo JL, Galán JF, Rosete A, de Lago A, Oliva I, González-de la Parra M, et al. Bioavailability of two single-dose oral formulations of omeprazole 20 mg: an open-label, randomized sequence, two-period crossover comparison in healthy Mexican adult volunteers. *Clin Ther.* 2008;30(4):693-9.
3. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. *Curr Gastroenterol Rep.* 2008;10(6):528-34.
4. Oosterhuis B, Jonkman JHG. Omeprazole: Pharmacology, Pharmacokinetics and Interactions. *Digestion*. 1989;44(suppl 1):9-17.
5. Choudhury A, Das S, Bahadur S, Saha S, Roy A. Formulation and evaluation of omeprazole tablets for duodenal ulcer. *Indian J Pharm Sci.* 2010;72(4):491-4.
6. Liu J, Shentu JZ, Wu LH, Dou J, Xu QY, Zhou HL, et al. Relative bioavailability and pharmacokinetic comparison of two different enteric formulations of omeprazole. *J Zhejiang Univ Sci B*. 2012;13(5):348-55.
7. Naesdal J, Andersson T, Bodemar G, Larsson R, Regårdh CG, Skånberg I, et al. Pharmacokinetics of [14C]omeprazole in patients with impaired renal function. *Clin Pharmacol Ther*. 1986;40(3):344-51.
8. Cederberg C, Andersson T, Skånberg I. Omeprazole: pharmacokinetics and metabolism in man. *Scand J Gastroenterol Suppl.* 1989;166:33-40.
9. Regårdh CG. Pharmacokinetics and metabolism of omeprazole in man. *Scand J Gastroenterol Suppl.* 1986;118:99-104.

10. Abelö A, Andersson TB, Antonsson M, Naudot AK, Skånberg I, Weidolf L.. Stereoselective metabolism of omeprazole by human Cytochrome P450 enzymes. *Drug Metab Dispos.* 2000;28(8):966-72.
11. Gebeyehu E, Engidawork E, Bijnsdorp A, Aminy A, Diczfalusy U, Aklillu E. Sex and CYP3A5 genotype influence total CYP3A activity: high CYP3A activity and a unique distribution of CYP3A5 variant alleles in Ethiopians. *Pharmacogenomics J.* 2011;11(2):130-7.
12. Tomalik-Scharte D, Lazar A, Fuhr U, Kirchheiner J. The clinical role of genetic polymorphisms in drug-metabolizing enzymes. *Pharmacogenomics J.* 2008;8(1):4-15.
13. Horn JR, Howden CW. Review article: similarities and differences among delayed-release proton-pump inhibitor formulations. *Aliment Pharmacol Ther*. 2005;22 Suppl 3:20-4.
14. Richards JP, Gimeno M, Moreland TA, McEwen J. A relative bioavailability study of 2 oral formulations of omeprazole after their administration in repeated doses to healthy volunteers. *Gastroenterol Hepatol*. 1999;22(4):171-5.
15. Hussein RF, Lockyer M, Hammami MM. Bioequivalence assessment of two capsule formulations of omeprazole in healthy volunteers. Arzneimittelforschung. 2007;57(2):101-5.
16. Rowland M, Tozer TN. Clinical pharmacokinetics. Concepts and applications. 3rd Edition. Philadelphia: Lippincott Williams & Wilkins. 1995.
17. Thomson AB, Sinclair P, Matisko A, Rosen E, Andersson T, Olofsson B. Influence of food on the bioavailability of an enteric-coated tablet formulation of omeprazole 20 mg under repeated dose conditions. *Can J Gastroenterol*. 1997;11(8):663-7.
18. Thomson AB, Kirdeikis P, Lastiwka R, Röhss, K, Sinclair P, Olofsson B. Pharmacokinetics and pharmacodynamics during treatment with the omeprazole 20 mg enteric-coated tablet and 20 mg capsule in asymptomatic duodenal ulcer patients. *Can J Gastroenterol*. 1997;11(8):657-60.
19. Vaz-da-Silva M, Loureiro AI, Nunes T, Maia J, Tavares S, Falcao A, et al. Bioavailability and bioequivalence of two enteric-coated formulations of omeprazole in fasting and fed conditions. *Clin Drug Investig*. 2005;25(6):391-9.
20. Declaration of Helsink (1994). *BMJ*. 1996;313:1448.
21. Boussery K, De Smet J, De Cock P, Vande Velde S, Mehuys E, De Paepe P, et al. Pharmacokinetics of two formulations of omeprazole administered through a gastrostomy tube in patients with severe neurodevelopmental problems. *Br J Clin Pharmacol.* 2011;72(6):990-6.
22. Litalien C, Theoret Y, Faure C. Pharmacokinetics of proton pump inhibitors in children. *Clin Pharmacokinet.* 2005;44(5):441-66.
23. Qiao HL, Hu YR, Tian X, Jia LJ, Gao N, Zhang LR, et al. Pharmacokinetics of three proton pump inhibitors in Chinese subjects in relation to the CYP2C19 genotype. *Eur J Clin Pharmacol*. 2006;62(2):107-12.
24. Pabst G, Jaeger H. Review of methods and criteria for the evaluation of bioequivalence studies. *Eur J Clin Pharmacol*. 1990;38(1):5-10.
25. Steinijans VW, Hauschke D, Jonkman JHG. Controversies in bioequivalence studies. *Clinical Pharmacokinetics*. 1992;22(4):247-53.
26. Allegrini A, Nuzzo L, Scaringi AT, Felaco S, Pavone D, Toniato E, et al. Bioequivalence study of two capsule formulations of omeprazole in healthy volunteers. *Arzneimittelforschung*. 2008;58(8):385-8.
27. Rhim SY, Park JH, Park YS, Lee MH, Hwang KG, Kim YS, et al. Pharmacokinetics and bioequivalence of 20 mg omeprazole capsule in 24 healthy Korean male volunteers. *Int J Clin Pharmacol Ther*. 2009;47(1):23-9.