Journal of
Bioequivalence & Bioavailability
ISSN: 0975-0851

Ponce-Navarrete et al., J Bioequiv Availab 2015, 7:4
DOI: 10.4172/jbb.1000233

Research Article Open Access

Bioavailability of Two Different Tablet Formulations of Telmisartan of Two Different Strengths (40 mg and 80 mg) in Healthy Male Mexican Volunteers

Daniel Ponce-Navarrete[1], Armando Cortés-Mendoza[1], Ericka López-Bojórquez[2], Jessica González-Bañuelos[2], Victoria Burke-Fraga[2] and Mario González-de la Parra[2]

[1]*Biodextra, S.A. de C.V., Mexico City, Mexico*
[2]*Biokinetics, S. A. de C. V., Mexico City, Mexico*

Abstract

Telmisartan is a non-peptide angiotensin II receptor antagonist. In Mexico, it is indicated for the treatment of arterial hypertension and for the prevention of morbidity and mortality of patients ≥ 55 years old with high risk of cardiovascular disease. The aim of these two studies was to compare the bioavailability and to determine the bioequivalence of two test formulations containing 40 mg and 80 mg of oral telmisartan. Two separate, single-dose, single-blind, randomized, two-period, crossover studies were conducted. For each study a different set of 30 male subjects completed both studies with a 14-day washout period. In both studies, the study formulations were administered after a 10-hour overnight fast. For pharmacokinetic analysis, blood samples were drawn at baseline, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours after administration. Plasma concentrations of telmisartan were determined using HPLC coupled with a fluorescence detector. The test and reference formulations were considered bioequivalent if the 90% CI for the geometric mean test/reference ratios were within the predetermined ranges of 80% to 125%.for AUC_{0-t} and $AUC_{0-\infty}$; and 75% to 133% for C_{max}. In the study with telmisartan 40 mg, the 90% CI were 81.23%; 104.94% for C_{max}, 92.61%; 115.41% for AUC_{0-t}, 91.83%; and 115.05% for $AUC_{0-\infty}$. In the study with telmisartan 80 mg the 90% CI were 86.84%; 121.07% for C_{max}, 90.51%; 110.38% for AUC_{0-t}, 90.58%; and 110.96% for $AUC_{0-\infty}$. In both studies, a single dose of the test formulation met the regulatory requirements to assume bioequivalence, based on the rate and extent of absorption.

Keywords: Telmisartan; Bioequivalence; Bioavailability; Pharmacokinetics; HPLC; Fluorescence

Introduction

Telmisartan is a non-peptide angiotensin II receptor antagonist [1,2]. In Mexico, it is indicated for the treatment of arterial hypertension and for the prevention of morbidity and mortality of patients ≥ 55 years old with high risk of cardiovascular disease [3].

The pharmacokinetics of orally administered telmisartan is nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations with increasing doses. Food has a minimal effect on its bioavailability [4].

Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours and it is mainly excreted via the feces and only to a very minor extent (<1%) by the kidney [5-7].

Telmisartan has been regarded as a highly variable drug with an intra-subject variability of C_{max} (%CV ≥ 30) [8].

The sponsor of these studies (Laboratorios Liomont, S. A. de C.V.) was interested in obtaining the marketing authorization for two dose strengths of telmisartan (40 mg and 80 mg), as oral tablet formulations (test formulations) in Mexico.

Two separate studies were planned for each of the two telmisartan strengths because of the non-linear pharmacokinetics of telmisartan [4].

Only male subjects were recruited for both studies because it has been reported that the pharmacokinetics of telmisartan exhibits gender differences [4].

A search of PubMed, MEDLINE and Google data bases for literature published up to February of 2015, using the combination terms *telmisartan, bioequivalence, bioavailability, pharmacokinetics, 40 mg, 80 mg, Mexico, Mexican* and *population*, did not identify any published data concerning the bioavailability of either strength of oral telmisartan in the Mexican population.

Therefore, the aim of these studies was to compare the bioavailability and to determine the bioequivalence of two test formulations of oral telmisartan (Raas® 40 mg and 80 mg tablets, Laboratorios Liomont, SA de CV, Mexico City, Mexico), containing telmisartan with their corresponding two reference drug formulations: Micardis® tablets (Boehringer Ingelheim Promeco, S.A. de C.V., Mexico City, Mexico), for the purpose of obtaining marketing authorization of the two test formulations in Mexico.

Subjects, Materials and Methods

The two protocols, TLMS-LMNT-02 (telmisartan 40 mg study) and TLMS-LMNT-05 (telmisartan 80 mg study) and their corresponding informed-consent forms were reviewed and approved by an independent ethics and research committee of Policlínicas Milenium (Mexico City, Mexico) on December 12, 2012 (telmisartan 40 mg study) and on May 15, 2012 (telmisartan 80 mg study). The corresponding

***Corresponding author:** Mario González-de la Parra, Biokinetics, S.A de C.V. Privada Jesúsdel Monte No.77,Col. Cuajimalpa, 05000 Mexico City, Mexico, E-mail: mdelaparra@biokinetics.com.mx

Received March 20, 2015; **Accepted** April 21, 2015; **Published** April 28, 2015

Citation: Ponce-Navarrete D, Cortés-Mendoza A, López-Bojórquez E, González-Bañuelos J, Burke-Fraga V, González-de la Parra M (2015) Bioavailability of Two Different Tablet Formulations of Telmisartan of Two Different Strengths (40 mg and 80 mg) in Healthy Male Mexican Volunteers. J Bioequiv Availab 7: 164-169. doi:10.4172/jbb.1000233

approvals by COFEPRIS (Federal Commission for Protection against Sanitary Risks) were obtained on February 15, 2013 and July 9, 2012, respectively. Both studies were conducted in accordance with the principles of the Helsinki Declaration and its amendments and the International Conference on Harmonisation Guideline for Good Clinical Practice.

For each study, the principal investigator informed the subjects of all procedures, the duration of the study, anticipated risks and discomfort it could entail, and an individual written informed consent was obtained prior to the initiation of the study. The studies were conducted from July to November, 2012 (telmisartan 80 mg study) and from May to September, 2013 (telmisartan 40 mg study).

Inclusion/Exclusion criteria

For each study, healthy Mexican male subjects aged 18 to 55 years were eligible for inclusion. Subjects were recruited from the clinical records retrieval of the volunteers database in Biodextra's Clinical Unit, Mexico City, Mexico.

Each potential participant had a physical examination. Classification of subjects as healthy was based on unremarkable findings obtained on a clinical health evaluation, which consisted of the following: a medical history; a complete physical examination (blood pressure, heart rate, weight, height, temperature and respiratory rate); and diagnostic testing that included a 12-lead ECG, chest radiography, and laboratory testing: hematology, chemistry panel, serological tests (hepatitis B and C, and HIV-1 and HIV-2 antibodies) and urinalysis. Systolic and diastolic blood pressure was measured with calibrated sphygmomanometers. The instrument cuff was applied to the right arm and the reading was taken with the subject in a seated position. Candidates were excluded if laboratory values were significantly out of the reference range and/or if all tests had not been completed. In both studies, laboratory testing was performed at the clinical unit. Before the enrollment of the participants, the laboratory data were reviewed by investigators at the clinical unit. Selected candidates were compensated for their participation.

Study design and drug administration

In both studies, a single-dose randomized-sequence, single-blind, two-period crossover design was used. The subjects for each study were admitted to the clinical site (Biodextra) on the day before the study was begun, and were randomly assigned by the principal investigator and verified by quality assurance personnel at the clinical unit to one of the two sequences, in a 1:1 ratio using a computer-generated table of random numbers.

For the telmisartan 40 mg study, the test formulation containing 40 mg of telmisartan (lot 198C0011; expiration date; March 31, 2014) was administered, followed by the reference drug formulation (Micardis®) containing 40 mg of telmisartan (lot 155544; expiration date August 31, 2014), or vice-versa.

For the telmisartan 80 mg study, the test formulation containing 80 mg of telmisartan (lot 198B0007; expiration date; October 31, 2013) was administered, followed by the reference drug formulation (Micardis®) containing 80 mg of telmisartan (lot 151014; expiration date January 31, 2014), or viceversa.

To ensure reliable baseline plasma measurements, participants underwent a 10-hour overnight fast with a 14-day washout period, which exceeds the seven half-lives required by the Federal Commission for Protection against Sanitary Risks (COFEPRIS) [9].

Blood samples were drawn for baseline plasma determinations in the following way. A 22-GA x 1.0 in (0.9 x 22 mm) indwelling angiocatheter (BD InSyte®, Becton, Dickinson and Co., Sao Paulo, Brazil) was inserted in suitable forearm vein and a 7.5-ml blood sample was drawn into heparin-treated vacuum tube (Vacutainer®, Becton, Dickinson and Co., New Jersey, USA.).

Subjects were administered a single tablet (40mg or 80 mg) of the test or the reference formulation with 250 ml of water (whichever was applicable in the corresponding study). Additional blood samples were drawn at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours after administration.

During hospitalization, the subjects were under medical surveillance, and during the washout period, participants maintained contact with the investigators to report any adverse events (AEs).

Plasma was obtained by centrifugation (4000 rpm for 7 minutes at room temperature) and stored at -70°C ± 5°C (until they were transported to the analytical unit (Biokinetics), where they were stored at -75°C ± 5°C until they were analyzed). After a 14-day washout period, participants returned to the clinical unit, where the alternative formulation was administered as in the first treatment period.

Subjects were asked to refrain from water and food intake for three hours after the study drug administration. Their diet, for each study and treatment period, consisted of three standardized meals (2353 kcal/d for the telmisartan 40 mg study and 2317 kcal/d for the telmisartan 80 mg study), at 3, 8 and 13 hours after the study drug administration.

Determination of telmisartan plasma concentrations

Chemicals: Telmisartan (lot: F0I345) and naproxen sodium (lot: J0C379) reference standards were obtained from USP (Rockville, MD) and used for the 40 mg and 80 mg studies. All solvents were HPLC grade (Avantor Performance Materials, Inc., Phillipsburg, NJ) and all reagents were analytical grade (Mallinkrodt Baker, Inc., Phillpsburg, NJ).

Method and Sample Preparation

In both studies, telmisartan plasma levels were determined by using a HPLC method developed and validated by personnel of Biokinetics in Mexico City, Mexico. The method included the following: 250 µl of plasma, 10 µl of internal standard (naproxen, 500 µg/ml) and 750 µl of acetonitrile. These components were vortexed in a 2.0-ml conical tube (Sarstedt AG & Co.) for 1 minute. The tube was centrifuged at 5000 rpm for 12 minutes at room temperature (25°C). The supernatant was separated and injected (volume of injection = 20 µl) into the chromatographic system (HPLC, Agilent Technologies, model 1100, Palo Alto, California).

Chromatographic conditions

In both studies, telmisartan concentrations were determined with a 150 × 4.6-mm internal-diameter column of 5-µm particle size (Zorbax®XDB –C18, Agilent Technologies, Palo Alto, California) equipped with a pre-column (12.5 × 4.6-mm internal-diameter column, 5-µm particle size, Zorbax® XDB –C18, Agilent Technologies) and eluted with a mobile phase consisting of a mixture (40:60 v/v) of an aqueous buffer solution (ammonium acetate, 10 mM; pH 3.0 ± 0.1) and acetonitrile. The column temperature was 25°C. Flow rate was maintained at 1 ml/minute and telmisartan detection was carried out using a fluorescence detector set at excitation and emission wavelengths of 300 nm and 385 nm, respectively. Typical retention

times for telmisartan and the internal standard were 3.8 and 2.7 minutes, respectively. The peak area was measured for calculation of the peak area ratio of telmisartan with respect to the internal standard, and the concentration was calculated.

Method validation

The method was validated in accordance with Mexican [9] and international guidelines [10]. The selectivity of the method was tested by the analysis of blank human plasma for six different subjects; blank human (hemolyzed and lipemic) plasma samples, as well as anticoagulants (heparin), xanthines (caffeine and theobromine), and other drug substances commonly used as analgesics (ibuprofen, diclofenac, paracetamol and acetylsalicylic acid). No interferences were observed in the resulting chromatograms.

The range of the method was 0.005 to 0.25 μg/ml, with lower limits of quantification and detection of 0.005 and 0.0025 μg/ml, respectively. The method was found to be linear within this range of concentrations with a coefficient of determination of 0.9969. The intra-assay %CV and accuracy (relative error) for telmisartan were 3.30% to 9.16% and -2.59% to -1.19%, respectively, while the inter-assay %CV and accuracy were 3.44% to 6.73% and -1.4% to 3.96%. The absolute recovery was above 95%.

Telmisartan in plasma was found to be stable after 24 hours at room temperature (25°C), after three freeze-thaw cycles and after 16 weeks at -75 ± 5°C. Quality control samples were prepared at three different concentration levels (designated as low (0.02 μg/ml), medium (0.075 μg/ml) and high (0.2 μg/ml)) of telmisartan independent of the calibration curve. This method was considered suitable by the investigators for both bioequivalence studies.

Tolerability

In both studies, tolerability was determined using clinical assessment, monitoring of vital signs (blood pressure, heart rate, armpit body temperature) at baseline, after the drug administration, during hospitalization, and at the end of the clinical stage of the studies. In addition, heart rate and blood pressure were measured after each blood sample was obtained. The subjects were interviewed (using open-ended questions) by the investigators during hospitalization and at the end of the clinical stage of the studies, concerning the occurrence of AEs. Subjects were asked to spontaneously report any AE to the investigators at any time during the studies, including the washout periods. Data for all AEs were recorded on a case report form. AEs that were life–threatening, led to death, hospitalization, disability, and/or medical intervention to prevent permanent impairment or damage were to be considered serious.

Pharmacokinetic and statistical analyses

Individual plasma concentration-time curves were constructed; C_{max} (maximum plasma drug concentration) and T_{max} (time to reach C_{max} after the administration of the drug) were directly obtained from these curves; the area under the plasma concentration-time curve from baseline to the last measurable concentration (AUC_{0-t}) was calculated according to the non-compartmental method using the trapezoidal rule. From the terminal log-decay phase, the elimination constant (k_e) was estimated using linear regression, and the apparent $t_{1/2}$ was estimated using the following equation [11].

$t_{1/2} = \ln 2/k_e$, where *ln* was defined as the natural logarithm. Extrapolation of AUC from baseline to infinity ($AUC_{0-\infty}$) was calculated as follows:

$AUC_{0-\infty} = AUC_{0-t} + C_t/k_e$, where C_t was the last measurable plasma concentration.

In both studies, to assess the bioequivalence between the test and reference formulations, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were considered as the primary variables. ANOVA for a 2 × 2 crossover design using log-transformed data for these parameters was carried out at the 5% significance level (α = 0.05).

The 90% CIs (confidence intervals) of the geometric means ratios (test/reference) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were calculated using log-transformed data. The test and the reference formulations were to be considered bioequivalent if the 90% CIs of AUC_{0-t} and $AUC_{0-\infty}$ fell within the predetermined range of 80% to 125%; for C_{max} if the 90% CI fell within the predetermined range of 75% to 133% (because telmisartan was regarded as a highly variable drug [8]); and if the probability of exceeding all of these acceptance limits was <0.05.

In both studies, sample size calculation [11] was based on the intra-subject variability of telmisartan C_{max} with an intra-subject %CV of 31% [12]. This calculation was performed considering the following values: 1-β=0.8, α=0.05, and an equivalence range of 75% to 133%, which yielded a sample size of 24 subjects for each study. Thus, the plan was to recruit 32 subjects in order to account for greater intra-subject %CV and potential subject dropouts.

All pharmacokinetic and statistical analyses were performed using WinNonlin version 5 (Pharsight, Mountain View, California).

Results

A total of 32 male subjects (mean (SD) age, 34 (12) years (range, 18-53 years); weight, 72.00 (10.23) kg (range, 55.00-93.50 kg); height, 169 (8) cm (range, 150-184 cm); and body mass index (BMI), 25.06 (2.95) kg/m^2(range, 19.94-31.36 kg/m^2) were enrolled and 30 completed the clinical stage of the study for telmisartan 40 mg. Two subjects were withdrawn from the study because one tested positive for drugs at the screening stage and the other one did not attend the first period of the clinical stage. Thus, the sample size for the evaluation of both PK parameters and tolerability was reduced from 32 subjects to 30 subjects.

A total of 32 male subjects (mean (SD) age, 33 (9) years (range, 21-55 years); weight, 70.61 (9.28) kg (range, 52.10-94.80 kg); height, 169 (7) cm (range, 155-188 cm); and body mass index (BMI), 24.78 (2.94) kg/m^2(range, 18.68-32.24 kg/m^2) were enrolled and 31 completed the clinical stage of the study for telmisartan 80 mg. One subject did not attend the first period of the study.

Because the plasma samples of another subject showed an unknown analytical interference at the retention time of the internal standard (naproxen) for both periods, this subject was withdrawn from the PK dataset. Thus the sample size for the evaluation of the PK parameters was reduced from 31 subjects to 30 subjects, whereas the 31 subjects remained available for the evaluation of tolerability.

It is important to point out that an investigation was conducted to determine the cause of this analytical interference. Although it yielded inconclusive results, it was hypothesized that the subject in question consumed OTC medications containing naproxen or naproxen sodium.

Pharmacokinetic parameters

Mean plasma concentration-time curves of the four telmisartan formulations are shown in Figure 1. This figure suggests comparable mean plasma concentration-time curves for each pair of reference/test

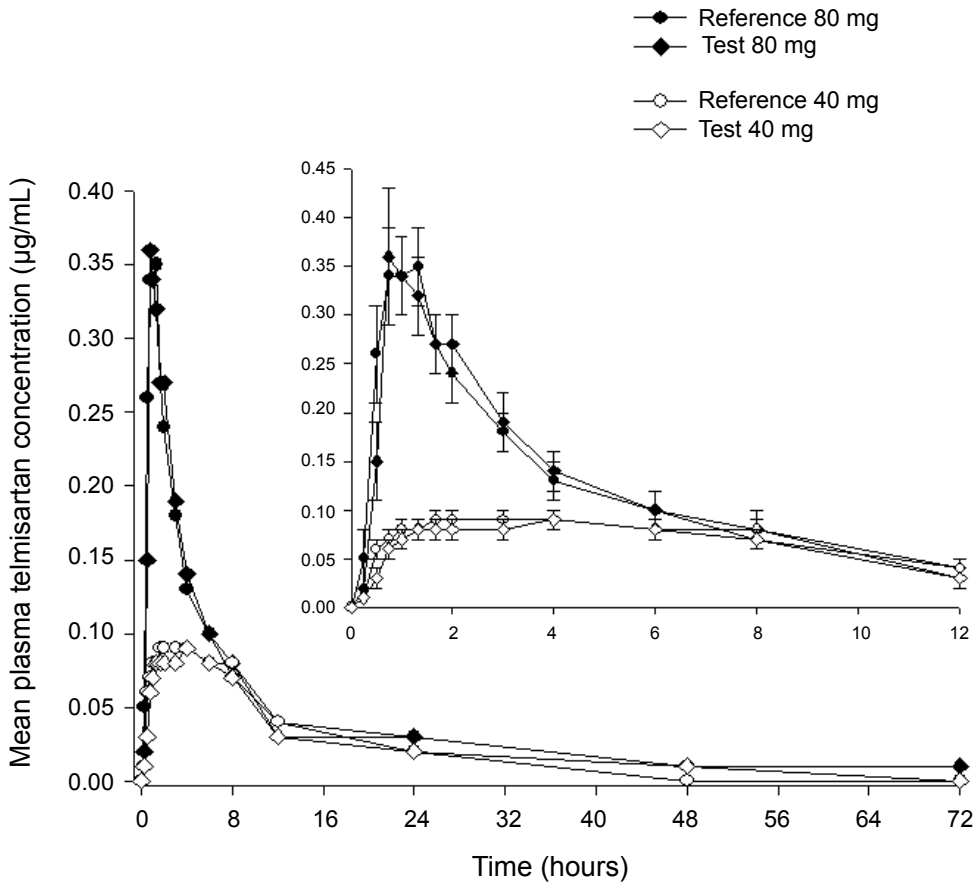

Figure 1: Mean plasma concentration-time curves of telmisartan after the administration of a single dose of telmisartan (40 or 80 mg). Solid symbols represent the reference/test pair of formulations containing telmisartan 80 mg (n = 30). Open symbols represent the reference/test pair of formulations containing 40 mg of telmisartan (n = 30). Right panel: mean (± SE) concentrations over the first 12 hours after administration. The trademarks were Micardis® (Boehringer Ingelheim Promeco, S. A. de C. V, Mexico City, Mexico) for the reference formulation and Raas® (Laboratorios Liomont, S.A. de C.V., Mexico City, Mexico) for the test formulation.

formulations corresponding to each study. In addition, it indicates a lack of dose proportionality in the pharmacokinetics of telmisartan, because when the dose was increased from 40 mg to 80 mg, the mean plasma concentration values for the telmisartan 80 mg formulations do not seem to exhibit the proportional increments that might have been expected by doubling the dose of telmisartan.

The pharmacokinetic parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, and apparent $t_{1/2}$) for the four telmisartan formulations are shown in Table 1. It is interesting to note that the all of the apparent- $t_{1/2}$ values were shorter than the reported terminal $t_{1/2}$ of telmisartan of approximately 24 hours. This is because the non-compartmental method, used in bioequivalence studies, is not suitable for the estimation of half-lives of bi-exponential elimination processes [13].

No significant period or sequence effects were detected for any of the PK parameters in either study, using ANOVA of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$(data not provided).

Table 2 shows the bioequivalence statistics (using the log-transformed data of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$): geometric mean ratios (test/reference) (90% CI); the probabilities of exceeding the limits of acceptance for bioequivalence; and the intra-subject %CV.

In both studies, all 90% CIs of the geometric mean ratios of AUC_{0-t} and $AUC_{0-\infty}$ fell within the predetermined range of 80% to 125%; all 90% CIs of the geometric mean ratios of C_{max} fell within the predetermined range of 75% to 133% (they even fell within the range of 80% to 125%). All probability values were <0.05. These results indicate that the bioequivalence criteria were met in both studies.

Tolerability

No serious adverse events were reported during these studies. For the telmisartan 40 mg study, 27 of the 30 subjects reported a total of 59 AEs. These included 51 blood-pressure reductions, 27 after the administration of the reference formulation and 24 after the administration of the test formulation. Other AEs included three headaches, two after the administration of the reference formulation and one after the administration of the test formulation; one case of diarrhea after the administration of the reference formulation; one of dizziness after the administration of the test formulation; one of adynamia (general weakness) after the administration of the test formulation, one of somnolence after the administration of the test formulation; and one of xerostomia (dry mouth sensation) after the administration of the test formulation. All of the AEs resolved spontaneously and all of them were regarded as mild in severity.

For the telmisartan 80 mg study, 27 of the 31 subjects reported a total of 45 AEs. These included 39 cases of blood-pressure reduction, 19 after the administration of the reference formulation and 20 after the administration of the test formulation; four headaches, two after

	40 mg		80 mg	
Parameter	Reference†	Test*	Reference†	Test*
No. of subjects	30	30	30	30
C_{max}, µg/ml	0.13 (0.06)	0.12 (0.06)	0.47 (0.29)	0.48 (0.33)
AUC_{0-t}, h·µg/ml	1.32 (1.02)	1.40 (1.14)	2.35 (2.28)	2.40 (2.51)
$AUC_{0-\infty}$, h·µg/ml	1.85 (1.33)	2.04 (1.53)	2.88 (2.73)	3.02 (2.98)
T_{max}, h	2.71 (1.89)	3.32 (2.38)	1.09 (0.55)	1.31 (0.57)
Apparent $t_{1/2}$, h	10.81 (8.67)	14.17 (12.50)	11.73 (11.82)	12.41 (14.52)

AUC_{0-t} = AUC from time 0 (baseline) to the last measurable concentration
$AUC_{0-\infty}$ = AUC from baseline extrapolated to infinity
*Trademark: Raas® (Laboratorios Liomont, S.A. de C.V., Mexico City, Mexico)
†Trademark: Micardis® (Boehringer Ingelheim Promeco, S.A.de C.V.,Mexico City, Mexico)

Table 1: Pharmacokinetic parameters of telmisartan after a single-dose administration of telmisartan (40 mg or 80 mg) in healthy Mexican male subjects. Values are expressed as means (SD).

Parameter	Geometric Mean Ratio (%)	90% CI	Probability of Exceeding Limits of Acceptance (lower; upper)		Intra-subject %CV
Telmisartan 40 mg					
C_{max}	92.32	81.23; 104.94	<0.01	<0.01	29.7
AUC_{0-t},	103.39	92.61; 115.41	<0.01	<0.01	25.4
$AUC_{0-\infty}$	102.79	91.83; 115.05	<0.01	<0.01	24.6
Telmisartan 80 mg					
C_{max}	102.53	86.84; 121.07	<0.01	<0.01	39.1
AUC_{0-t},	99.96	90.51; 110.38	<0.01	<0.01	22.8
$AUC_{0-\infty}$	100.25	90.58; 110.96	<0.01	<0.01	22.9

AUC_{0-t} = AUC from time 0 (baseline) to the last measurable concentration
$AUC_{0-\infty}$ = AUC from baseline extrapolated to infinity
*The limits of acceptance of C_{max} (for both studies) are from 75% to 133%, whereas the limits of acceptance for both AUC_{0-t} and $AUC_{0-\infty}$ are from 80% to 125%.

Table 2: Geometric mean ratios, 90% CIs, the probabilities of exceeding the limits of acceptance and the intra-subject %CV of the pharmacokinetic parameters determined for telmisartan after a single-dose administration of telmisartan (40 mg or 80 mg) in healthy male Mexican subjects.

the administration of the reference formulation and two after the administration of the test formulation; and two cases of dizziness after the administration of the test formulation. All of the AEs resolved spontaneously and all of them were regarded as mild in severity.

Discussion

The results of the two studies suggest that each pair of reference/test formulations (telmisartan 40 or 80 mg) was not statistically different in terms of their PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$). In addition, they suggest that no clinically important differences exist for T_{max} and $t_{1/2}$ between each pair of reference/test formulations (based on means and standard deviations).

Considering that all 90% CIs of the ratios of the pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were found to be within the predetermined ranges of bioequivalence and that the two one-sided *t*tests found all of the probability values to be <0.05, the results of both studies satisfied the accepted regulatory requirements to assume bioequivalence.

In addition, the mean plasma concentration-time curves for the two telmisartan dose strengths are consistent with the reported nonlinear pharmacokinetics of telmisartan [4].

In both studies, none of the reported AEs was considered serious.

Limitations

As with any clinical trial, and in particular for most bioavailability studies, these studies have some limitations that should be considered. First, this is a single-blind study, so it might not objectively address the effectiveness and safety profiles of the formulations tested. The data were obtained from healthy subjects, in accordance with regulatory requirements [9], within a specific gender (male) and age range, who were administered a single dose; the PK parameters might differ in target populations. For example, differences in absorption, distribution, metabolism and excretion of the drug might exist in patients, with respect to healthy subjects. Thus, the results of these studies might not be generalizable to a target population.

In addition, these studies were conducted under fasting conditions because the bioavailability of telmisartan has been reported not to be significantly affected by the concomitant intake of food [4]. However, further studies would be useful in assessing the effect of food on the bioavailability of this drug for a target population.

Because of the limited data (small sample size, single dose, healthy male subjects, age range, and fasting conditions) in the present studies, we are unable to predict the response of the drug at any time following alternative doses and/or administration intervals with the present dataset. Further studies are needed to compare the test formulations with the reference formulations in Mexican patient groups. The results of these studies might serve as a reference for future controlled studies of the drug in the Hispanic population.

Conclusions

In these two studies of healthy, fasting, male Mexican subjects, who received a single dose of either the test or reference formulation, it was concluded that the test formulations of telmisartan 40 mg and 80 mg met the Mexican regulatory requirements to assume bioequivalence, based on the rate and extent of absorption. These formulations were also well tolerated.

Acknowledgments

This research and its publication were supported by Laboratorios Liomont, S.A. de C.V., Mexico City, Mexico. The authors have indicated that they have no other conflicts of interest regarding the content of the article.

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