

Bioavailability of Two Tablet Formulations of a Single Dose of Moxifloxacin 400 mg: An Open-Label, Randomized, Two-Period Crossover Comparison in Healthy Mexican Adult Volunteers

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Abstract

Moxifloxacin is a synthetic fluoroquinolone with a broad spectrum of antibacterial activity. It is indicated for the treatment of respiratory tract, skin and intra-abdominal infections.

The aim of this study was to compare the bioavailability and to determine the bioequivalence of a test and reference formulation of oral moxifloxacin 400 mg, administered as a tablet, and to generate data regarding the oral bioavailability of this drug in Mexican population.

This single-dose, randomized-sequence, open-label, two-period, crossover study was conducted on a total of 26 healthy Mexican adult subjects of both genders, with an eight-day washout period. Study formulations were administered after a 10-hour overnight fast. For pharmacokinetic analysis, blood samples were drawn at 0 (baseline), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48 and 72 hours after administration. Plasma concentrations of moxifloxacin were determined using HPLC coupled with a fluorescence detector. The test and reference formulations were considered bioequivalent if the 90% CIs for the geometric mean test/reference ratios were within a predetermined range of 80% to 125%.

The 90% CIs for the geometric mean ratios of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were 88.67% to 108.70%, 97.44% to 102.50%, and 97.70% to 104.82 %, respectively.

In this study a single dose of the test formulation met the regulatory requirements for assuming bioequivalence, based on the rate and extent of absorption.

Keywords: Moxifloxacin; Bioequivalence; Bioavailability; Pharmacokinetics; HPLC

Introduction

Moxifloxacin hydrochloride is a synthetic fluoroquinolone antibacterial agent with a broad spectrum of activity, encompassing Gram-negative and Gram-positive bacteria, indicated for the treatment of respiratory infections [1,2].

Moxifloxacin is well absorbed following oral administration with an absolute bioavailability of 91.8%. [3].

Its mean elimination half-life is approximately 12 hours under steady-state conditions [4].

Moxifloxacin shows linear pharmacokinetics after single doses ranging from 50 to 800 mg [5] and its bioavailability is not affected by the concomitant intake of food [6].

The reference tablet formulation (Avelox[®], Bayer de México, S.A. de C.V, Mexico City, Mexico) is marketed in Mexico. It was selected as the reference formulation because it is included in the list of Drug Reference Medications issued by the Mexican Federal Commission for the Protection against Sanitary Risks (COFEPRIS). It is important to point out that the reference medications (formulations) are indicated in a list that is mandatory for bioequivalence studies performed in Mexico.

The test formulation (Zinolox 4G[®], Laboratorios Liomont, S. A. de C. V., Mexico City, Mexico) was selected because the sponsor of the present study wanted to obtain its marketing authorization in Mexico.

A search of PubMed, MEDLINE and Google data bases for literature published up to May of 2014, using the combination terms *moxifloxacin*, *bioequivalence*, *bioavailability*, *pharmacokinetics*, *Mexico*, *Mexican* and *population*, did not identify any published data concerning the bioavailability of oral moxifloxacin in the Mexican population.

Therefore, the aim of this study was to compare the bioavailability and to determine the bioequivalence of a test and reference formulation of oral moxifloxacin 400 mg and to generate data regarding its bioavailability in the Mexican population for the purpose of obtaining the marketing authorization of the test formulation in Mexico.

Subjects, Materials and Methods

The study protocol (P455S026V006) and the informed-consent

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form were approved by an independent ethics and research committee (Comité de Ética e Investigación para Estudios en Humanos, Mexico City, Mexico) on October 10, 2012 and by COFEPRIS (Federal Commission for Protection against Sanitary Risks) on December 11, 2012. The study was conducted in accordance with the ethical principles of Helsinki and its amendments and the International Conference on Harmonisation for Good Clinical Practice Guideline.

The principal investigator informed the subjects of all processes, 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 procedures. The study was conducted from January to May of 2013.

Inclusion/exclusion criteria

Healthy Mexican adults aged 18 to 55 years and of either gender were eligible for inclusion in the study. Subjects were recruited from the volunteers' database at the Center of Pharmacological and Biotechnology Research (clinical unit) in Medica Sur Hospital, Mexico City, Mexico.

A clinical assessment was performed on each potential participant. Classification of the subjects as healthy was based on clinical health evaluation, which consisted of the following: a personal interview, a complete physical examination, vital signs (blood pressure (BP), heart rate, weight, height, temperature and respiratory rate); and diagnostic testing that included a 12-lead ECG, chest radiography, and laboratory hematology and chemistry panel, serological tests for hepatitis B, C and HIV antibodies, urinalysis, and a pregnancy test in women. Systolic and diastolic BP were measured with a qualified sphygmomanometer (Tycos; Welch Allyn, Skaneateles Falls, NY). The BP 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. Laboratory testing was performed at Medica Sur Laboratory, which has been certified by the Mexican government and the College of American Pathologists. The scope of the certifications included the tests relevant to this study. Before the enrollment of the participants, the laboratory data were reviewed by investigators. Selected candidates were compensated for their time dedicated to participation and transportation.

Study design and drug administration

A single-dose randomized-sequence, open-label, two-period, crossover design was used. A total of 26 subjects (21 men, 5 women) were admitted to the clinical site on the day before the study was begun and were randomly assigned by a pharmacist in the presence of quality assurance personnel in a 1:1 ratio, using a validated computer-generated table of random numbers, to one of the two sequences (test formulation containing moxifloxacin hydrochloride equivalent to 400 mg of moxifloxacin [lot 234C0010; expiration date December 2014] followed by the reference formulation containing moxifloxacin hydrochloride equivalent to 400 mg of moxifloxacin [lot XB104B4; expiration date May 2014], or vice versa). Randomization codes were concealed from all the investigators of the study.

To ensure reliable baseline plasma measurements, participants underwent a 10-hour overnight fast with an eight-day washout period, which exceeds the seven half-lives required by COFEPRIS.

Blood samples were drawn for baseline plasma determinations in the following way. A 18-G × 1.6 in (1.1 × 30 mm) peripheral intravenous catheter (BD-InSyte, Becton, Dickinson and Co., Sao Paulo, Brazil) was

inserted in a suitable forearm vein and a 7.5ml blood sample was drawn into a heparin-treated vacuum tube (S-Monovette, Sarstedt AG & Co., Nümbrecht, Germany).

Subjects were administered a single tablet of the test or the reference formulation with 250 ml of water. Additional blood samples were drawn at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48 and 72 hours after administration.

Plasma was obtained by centrifugation (1000 g for 15 minutes at 25°C) and stored at -75°C ± 10°C until analyzed using HPLC. After an eight-day washout period, participants returned to the clinical unit, where the alternative formulation was administered keeping the same conditions as in the first treatment period.

Subjects were asked to refrain from water and food intake for three hours after study drug administration. Their diet, for each treatment period, consisted of three standardized meals (2235.6 kcal/d) at 3.25, 6.5 and 12.75 hours after study drug 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).

Determination of moxifloxacin plasma concentrations

Chemicals: Moxifloxacin hydrochloride (lot: F0H454, purity 95.9%) reference standard was obtained from USP (Rockville, MD). All solvents were HPLC grade and all reagents were analytical grade.

Method and Sample Preparation: Moxifloxacin 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 (telmisartan, 3000 µg/ml) and 750 µl of acetonitrile. These components were vortexed in a 2.0 ml conical tube, (Sarstedt AG & Co.) for one minute. The tube was centrifuged at 8000 rpm for five 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

Moxifloxacin concentrations were determined with a 150 × 4.6 mm internal-diameter column of 3.5 µm particle size (Zorbax® Eclipse XDB-Phenyl, 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 the moxifloxacin was detected by a fluorescence detector (Agilent Technologies) set at an excitation wavelength of 296 nm and emission wavelength of 504 nm. Typical retention times for moxifloxacin and the internal standard were two and four minutes, respectively. The peak area was measured for calculation of the peak area ratio of moxifloxacin with respect to the internal standard, and the concentration was calculated.

Method validation

The analytical method was validated according to Mexican [7] and international guidelines [8].

The *selectivity of the method was tested* by the analysis of blank human plasma samples from 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 (*acetylsalicylic acid, ibuprofen, diclofenac, paracetamol and naproxen*). No interferences were observed in the resulting chromatograms.

The range of the method was 0.07 to 2.0 µg/ml, with lower limits of quantification (LLOQ) and of detection (LLOD) of 0.07 and 0.035 µg/ml, respectively. The method was found to be linear within this range of concentrations with a coefficient of determination of 0.99. The intra-assay %CV and accuracy (relative error) for moxifloxacin were 1.22% to 3.23% and -9.28% to 3.16%, respectively, while the inter-assay %CV and accuracy were 5.08% to 5.90% and -2.25% to -0.64%. The absolute recovery was above 93.8%.

Moxifloxacin 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 (QC) samples were included in every analytical run to verify its performance. These QC samples were prepared at three different concentration levels (designated as low, (0.15 µg/ml), medium (0.75 µg/ml) and high (1.5 µg/ml)) of moxifloxacin independent of the calibration curve. This method was considered suitable by the investigators for the bioequivalence study of moxifloxacin.

Tolerability

Tolerability was determined using clinical assessment, monitoring of vital signs at baseline, after the drug administration during hospitalization, and at the end of the clinical stage of the study.

The subjects were interviewed (using open-ended questions) by the investigators during trial conduction and at the end of the clinical stage of the study, concerning the occurrence AEs. Subjects were asked to spontaneously report any AE to the investigators at any time during the study, including the washout period. 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 considered serious.

Pharmacokinetic and statistical analyses

Sample size calculation [9] was based on the within-subject variability of moxifloxacin C_{max} with a %CV of 12.71% [10]. This calculation was performed considering the following values: $1 - \beta = 0.8$, $\alpha = 0.05$, %CV=12.71, and an equivalence range of 80% to 125%, yielded with a sample size of 10 subjects. In this study, a sample size of 26 subjects was used because, at the time the study was conducted, a minimum sample size of 24 subjects was required for bioequivalence studies by COFEPRIS.

Individual plasma concentration-time curves were constructed; C_{max} and T_{max} were directly obtained from these curves, the area under the plasma concentration-time curve from time baseline to the last measurable concentration (AUC_{0-t}) was calculated by a non-compartmental method using the trapezoidal rule. From the terminal log-decay phase, the elimination rate constant (k_e) was estimated using linear regression, and the $t_{1/2}$ was estimated using the following equation [9]:

$t_{1/2} = \ln 2 / k_e$ 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.

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 ($\alpha = 0.05$).

The 90% CIs of the geometric mean 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 considered bioequivalent if the 90% CIs of these parameters fell within a predetermined range of 80% to 125% and if the probability of exceeding these limits was <0.05. The probability of exceeding the 80% to 125% range was obtained using the two one-sided tests procedure described by Schuirmann [11]. All pharmacokinetic and parametrical-statistical analyses were performed using Win Nonlin Version 5 (Pharsight, Mountain View, California).

Results

A total of 26 subjects (21 men, 5 women; mean [SD] age, 34 [11] years [range, 19-51 years]; weight, 66.12 [6.11] kg [range, 53.10-77.70 kg]; height, 1.67 [0.08] m [range, 1.47-1.81 m]; and body mass index [BMI], 23.74 [1.55] kg/m² [range, 20.04-25.96 kg/m²]) were enrolled and completed the clinical stage of the study.

Pharmacokinetic parameters

Mean plasma concentration-time curves of the two moxifloxacin formulations are shown in Figure 1. As can be seen in this figure, both curves look similar.

Table 1 shows the pharmacokinetic parameters (C_{max} , T_{max} , $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$) for two data sets: the full data set and the reduced data set. The full data set consists of all of the subjects, including all of their moxifloxacin-concentration values. The reduced data set also consists of all of the subjects, with the single exception of an outlier concentration value (1.74 µg/mL) for one of the subjects (subject 12, when the reference formulation was administered).

This outlier was found at the last time point (72 hours), where concentration values below the LLOQ was expected. It is important to point out that an internal investigation was conducted and the results regarding the origin of the outlier were inconclusive. Therefore, it was decided to evaluate its potential impact on the estimation of the pharmacokinetic parameters, as well as on the results of the bioequivalence analysis.

In comparing both data sets, it can be seen that the effect of the outlier was to inflate the means and standard deviations of the $AUC_{0-\infty}$ and $t_{1/2}$ values for the reference formulation. It can be noted that, when this outlier was excluded from the estimation (reduced data set), both means and standard deviations for these parameters were reduced to more comparable values between the two formulations.

No significant formulation or period-sequence effects (data not provided) were detected based on ANOVA of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ (for both data sets). The estimated intra-subject %CVs for the full data set were 21.70, 7.05 and 25.99, respectively; for the reduced data set they were 21.70, 5.33 and 7.42.

Table 2 shows the bioequivalence statistics for both data sets (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 power values of the test.

The 90% CIs for moxifloxacin C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for the full data set were 88.67% to 108.70%, 94.32% to 100.84%, and 82.23% to

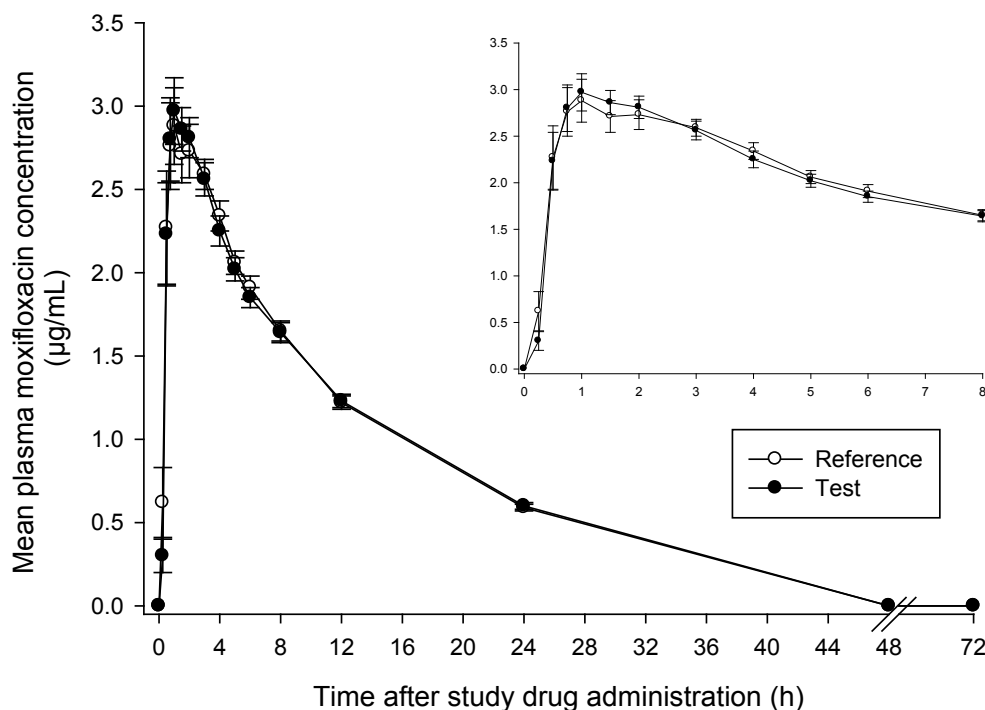


Figure 1: Mean plasma concentration-time curves after a single-dose administration of a test (trademark: Zinolox 4G®, Laboratorios Liomont, S. A. de C. V., Mexico) and a reference (trademark: Avelox®, Bayer de México, S. A. de C. V., Mexico City, Mexico) formulation of oral moxifloxacin 400 mg in healthy Mexican adult subjects (n = 26). Inset: mean (SE) over the first 8 hours after administration.

Parameter	Test†	Reference‡
Full data set		
C_{max}^* µg/ml	3.57 (0.85)	3.65 (0.94)
AUC_{0-t}^* µg·h /ml	33.91 (5.40)	34.87 (6.39)
$AUC_{0-\infty}^*$ µg·h/ml	43.73 (6.67)	52.96 (46.91)
T_{max}^* h	1.15 (0.75)	1.51 (1.19)
$t_{1/2}^*$ h	11.25 (1.58)	14.12 (15.79)
Reduced data set		
C_{max}^* µg/ml	3.57 (0.85)	3.65 (0.94)
AUC_{0-t}^* µg·h /ml	33.91 (5.40)	33.94 (5.58)
$AUC_{0-\infty}^*$ µg·h/ml	43.73 (6.67)	43.31 (7.35)
T_{max}^* h	1.15 (0.75)	1.51 (1.19)
$t_{1/2}^*$ h	11.25 (1.58)	10.85 (1.70)

The full data set includes all of the subjects, including all of their concentration values.

The reduced data set includes all of the subjects, with the single exception of the last concentration value (72-hours, reference formulation) for the subject identified as number 12.

AUC_{0-t}^* = AUC from time 0 (baseline) to the last measurable concentration;

$AUC_{0-\infty}^*$ = AUC from baseline extrapolated to infinity.

*Trademark: Zinolox 4G® (Laboratorios Liomont, S. A. de C. V., Mexico City, Mexico).

†Trademark: Avelox® (Bayer de México, S. A. de C. V., Mexico City, Mexico).

Table 1: Pharmacokinetic parameters of a test and a reference formulation of oral moxifloxacin 400 mg after a single administration in healthy Mexican adult subjects (n = 26). Values are mean (SD).

104.81%, respectively; and for the reduced data set they were 88.67% to 108.70%, 97.44% to 102.50% and 97.70% 104.82%. For both data sets, all 90% CIs of the geometric mean ratios of the three parameters fell within the predetermined range of 80% to 125%. All probability values were <0.05. All the power values were >0.8 (power >80%), suggesting that the sample size was sufficient for the purpose of the study.

These results indicated that the bioequivalence criteria were met, regardless of the exclusion of the outlier.

Tolerability

Seven of the 26 subjects reported a total of 12 AEs. The most commonly AE reported was dizziness (6 AEs), three after administration of the reference formulation and three after the administration of the test formulation.

Other AEs were headache (4 AEs), two after administration of the reference formulation, two after administration of the test formulation, and nausea (2 AEs), one after administration of the reference

Parameter	Geometric Mean Ratio, % (90% CI)	Probability of Exceeding Limits of Acceptance		Power
		$P < 80\%$	$P > 125\%$	
Full data set				
C_{max}	98.17 (88.67, 108.70)	<0.001	<0.001	0.97
AUC_{0-t}	97.53 (94.32, 100.84)	<0.001	<0.001	1.00
$AUC_{0-\infty}$	92.84 (82.23, 104.81)	0.023	<0.001	0.92
Reduced data set				
C_{max}	98.17 (88.67, 108.70)	<0.001	<0.001	0.97
AUC_{0-t}	99.94 (97.44, 102.50)	<0.001	<0.001	1.00
$AUC_{0-\infty}$	101.19 (97.70, 104.82)	<0.001	<0.001	1.00

The full data set includes all of the subjects, including all of their concentration values.

The reduced data set includes all of the subjects, with the single exception of the last concentration value (72-hours, reference formulation) for the subject identified as number 12.

AUC_{0-t} = AUC from time 0 (baseline) to the last measurable concentration;

$AUC_{0-\infty}$ = AUC from baseline extrapolated to infinity.

†Values were calculated from the natural logarithm-transformed data.

†Trademark: Zlinolox 4G® (Laboratorios Liomont, S. A. de C. V., Mexico City, Mexico).

‡Trademark: Avelox® (Bayer de México, S. A. de C. V., Mexico City, Mexico).

Table 2: Geometric mean ratios (90% CI) of pharmacokinetic parameters*, the probabilities of exceeding the predetermined limits of bioequivalence (80%-125%), and the power test results from a single-dose administration of a test† and a reference‡ formulation of oral moxifloxacin 400 mg in healthy Mexican adult subjects.

formulation, one after administration of the test formulation. Most were classified as mild and two as moderate (dizziness). All of the AEs were spontaneously resolved under medical surveillance.

None of the AEs was considered serious. In addition, all of these types of AEs have been previously reported with moxifloxacin treatment [12].

Discussion

For both data sets, all of the 90% CIs of the geometric mean ratios of the pharmacokinetic parameters (C_{max} , AUC_{0-t} and $AUC_{0-\infty}$) were found to be within the predetermined range of bioequivalence (80%-125%) and the Schuirmann tests (i.e., probability of exceeding limits of acceptance) found all of the probability values to be <0.05; these results satisfy the accepted regulatory requirements to assume bioequivalence.

Although the presence of the outlier did not affect the conclusion of bioequivalence, it did inflate the estimates of $AUC_{0-\infty}$ and $t_{1/2}$ for the reference formulation, as well as for both the intra-subject %CV values and the width of the 90% CI of AUC_{0-t} and $AUC_{0-\infty}$. Hence, it is important to consider the impact of outliers on the data analysis.

Both formulations were well tolerated, in view of that fact that none of the reported AEs by seven subjects was considered serious and all been previously reported.

Limitations

As with any clinical trial, and in particular with most bioavailability studies, the current study had some limitations that should be considered. First, this was an open-label study, so it might not objectively address the safety profiles of the formulations tested, but distribution of AEs was the same for both formulations.

The data were obtained from healthy adult subjects, in accordance

with regulatory requirements (COFEPRIS), within a specific age range, who were administered a single dose; the PK parameters of moxifloxacin might differ in target populations. For example, differences in absorption, metabolism and excretion of moxifloxacin might exist in patients, with respect to healthy subjects. Thus, the results of this study might not be generalizable to a target ill population.

In addition, this study was conducted under fasting conditions because the bioavailability of moxifloxacin has been reported not to be affected by the concomitant intake of food [6].

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

Conclusions

In this small study of healthy, fasting, Mexican adult subjects, single doses of oral moxifloxacin 400 mg met the Mexican (COFEPRIS) regulatory requirements to assume bioequivalence based on the rate and extent of absorption. Both formulations were well tolerated.

Acknowledgements

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