Bioequivalence Study Comparing Meloxicam 15mg Tablet of Pascual Laboratories, Inc. with Meloxicam (Mobic®) 15mg Tablet of Boehringer Ingelheim in Healthy Male Filipino Subjects under Fasting Conditions

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ABSTRACT

Objective. Proof of bioequivalence is important for the interchangeability of pharmaceutically equivalent drug products. This study aimed to compare the rate and extent of absorption of meloxicam 15 mg tablet of Pascual Laboratories, Inc. (Test) with meloxicam 15 mg tablet (Mobic) of Boehringer Ingelheim (Reference) in healthy Filipino men. In addition, the study also determined the safety and tolerability of single doses of the said medications, under the same conditions.

Methods. This was a randomized, open label, blind-endpoint analysis, truncated, crossover study with single drug doses administered in the fasting condition in each of the two treatment periods, separated by a two-week washout period. Pharmacokinetic blood sampling was performed up to 72 h post-dose. Plasma samples were analyzed using a validated liquid chromatography with tandem mass spectrometry technology. The primary endpoints were: area under plasma-concentration-time curve from time zero to the last observed concentration at time 72 h (AUC_{0-72}) and maximum plasma concentration (C_{max}) for meloxicam.

Results. Eighteen men (mean age 21.5 years; mean body mass index 22.9 kg/m^2) completed the study. When administered one meloxicam 15 mg tablet, the ratios of the geometric means of the primary endpoints AUC_{0-72} and C_{max}, were within the established bioequivalence limits of 80% to 125% compared with Mobic 15 mg tablet: 104.07% (90% Confidence Interval [CI]: 100.26, 108.03), and 103.34% (90% CI: 96.22, 110.97), respectively. No adverse event was reported.

Conclusion. Meloxicam 15 mg tablet of Pascual Laboratories, Inc. and the innovator Mobic 15 mg tablet are bioequivalent. Single doses of both products were safe and well tolerated.

Keywords: bioequivalence study, meloxicam, nonsteroidal anti-inflammatory drug

INTRODUCTION

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.[1] The main therapeutic effects of NSAIDs derive from their ability to inhibit prostaglandin (PG) production. The first enzyme in the PG synthetic pathway is cyclooxygenase (COX), also known as PG G/H synthase.[2] There are 2 forms of COX: COX-1 and COX-2. Meloxicam inhibits both COX-1 and COX-2, with preferential binding for COX-2.[3]

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Meloxicam is available in 7.5 mg and 15 mg tablet formulations. In adults, the maximum recommended daily oral dose is 15 mg. It is well absorbed after oral administration with an absolute bioavailability of 89%.[4-6] Meloxicam reaches maximum plasma concentration (C_{max}) at 9–11 h after a 30 mg dose and at 2.5 to 7 h after a 15 mg dose. The mean volume of distribution is approximately 10 L. It is ~99.4% bound to plasma proteins within the therapeutic dose range.[7] Meloxicam concentrations in synovial fluid, after a single oral dose, range from 40% to 50% to those in the plasma. It is extensively metabolized in the liver and excreted in the urine and feces.[4]

In the Mobic® clinical trial database, gastrointestinal adverse events were the most frequently reported adverse events that manifested as: abdominal pain, diarrhea, constipation, dyspepsia, flatulence, nausea, and vomiting. Other reported adverse events include edema, influenza-like symptoms, dizziness, headache, arthralgia, pharyngitis, insomnia, and rash.[4,8,9]

This study was conducted in the Philippines to determine if the generic meloxicam 15 mg tablet of Pascual Laboratories, Inc. is bioequivalent to the reference meloxicam 15 mg tablet (Mobic®) of Boehringer Ingelheim in compliance with regulatory requirements for the renewal of registration of Pascual Laboratories, Inc. specified by the Philippine FDA. In addition, the study also determined and compared the safety profile of single doses of both drug products.

METHODS

Study design

This bioequivalence study was a randomized, open label, blind-endpoint analysis, truncated, crossover, single dose study in healthy adult Filipino men under fasting conditions conducted in the clinical facility of Pharmalytics Corporation in Cavite, Philippines. The primary objective was to compare the rate and extent of absorption, or bioavailability, of Meloxicam 15 mg tablet (Pascual Laboratories, Inc., the Test product) with that of Meloxicam 15 mg tablet (Mobic®, of Boehringer Ingelheim, the Reference product). The secondary objective was to evaluate the safety and tolerability of single doses of both drug products. Safety is normally assessed by the presence of adverse events attributable to the drug while tolerability refers to the degree to which adverse effects of the drug can be tolerated by the patient. An adverse reaction (safety concern), such as dizziness or headache, may happen even after a single dose of the drug. It may be tolerable to one patient and intolerable to another depending on the subjective perceptions of the study participants.

The details of the test drugs are as follows: generic meloxicam 15 mg tablet manufactured by Pascual Laboratories, Inc. (Lot No.181029RD); and for the reference formulation, Mobic® 15 mg tablet manufactured by Boehringer Ingelheim Indonesia (Batch No. 17111297).

Screening was conducted at most 28 days and at least 2 days prior to the first dose of the study drug. Enrolled subjects were admitted and confined in the clinical facility of Pharmalytics Corporation the day before dosing and were discharged after the last pharmacokinetic (PK) sampling in each treatment period. They returned to the facility after 14 days for the second treatment period when the other study drug was administered. Subject safety was monitored through physical examination, hematology and blood chemistry tests and clinical interview for documentation of adverse events (AEs).[10] Final safety assessments were conducted seven days after the last PK sampling. The study was conducted from May to June 2018.

The protocol and informed consent form were reviewed and approved by the Ethics Review Board of University of the East Ramon Magsaysay Memorial Medical Center, Inc. Research Institute for Health Sciences (UERMMMCI-RIHS) prior to implementation. The study was conducted in compliance with all requirements of the International Council for Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), as well as the Declaration of Helsinki.[11]

Study participants

Healthy men aged 18 to 45 years with a body mass index of 18 to 27 kg/m^2, who provided signed informed consent were enrolled in the study. Subjects were considered healthy if they had no clinically relevant abnormalities based on medical history and physical examination.

Exclusion criteria were: any evidence or history of clinically significant cardiovascular, pulmonary, renal, hepatic, endocrine, hematological, psychiatric, neurologic disease; gastrointestinal disorders which may impair drug absorption; clinically significant deviation in chest x-ray, ECG, hematology and blood chemistry tests; positive pre-study urine drug screen; history of sensitivity to the study drug or related substances; use of any drug within 10 days prior to and during the study; current smoker or smoking within 10 days prior to study enrolment; history of regular alcohol consumption; subjects who could not abstain from food and/or beverages that contain caffeine or other xanthines; and participation in a clinical study within four weeks prior to the first study visit.

Eighteen subjects were enrolled in the study. This sample size was based on within subject standard deviation for the log AUC known from previously published studies and on the bioequivalence criterion (90% confidence that the estimated population mean ratio lies between 80% and 125%).[2,5,6,8,9]

Randomization and Interventions

Subjects under fasted conditions were randomly allocated to receive with 240 mL water one tablet of either test or reference product on the first treatment period and one tablet of the other drug administered on the second treatment period.

Outcome Measurement

In each treatment period, blood samples were extracted from the forearm vein into heparinized tubes at the following time-points: pre-dose; 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 12.00, 24.00, 36.00, 48.00 and 72.00 h post-dose. Each sample was centrifuged within 45 min of collection at approximately 3000 rpm for about 10 min at 15±2^{0}C, then plasma was transferred into micro centrifuge tubes and stored at -20^{0}C until assayed.

The primary pK parameters were AUC from time zero to the last observed concentration at time 72 h (AUC_{0-72}) and maximum plasma concentration (C_{max}). Secondary pK parameters were time to maximum plasma concentration (T_{max}), AUC from time zero extrapolated to infinite time (AUC_{0-inf}), half-life ($t_{1/2}$), and terminal elimination rate constant (K_{el}).

Info Kinetics (Penang, Malaysia) performed the pK analysis using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS; Agilent 1290) technology. This method was validated and demonstrated adequate sensitivity, specificity, linearity, recovery, accuracy and precision (inter and intra-assay variability). Plasma samples were dispensed in tubes and the internal standard solution (meloxicam-d3 4000ng/ml, 50 µL) was added. The sample was extracted by adding in 200 µL of 1.00 M hydrochloric acid and vortex-mixed for five seconds, followed by 2 mL of methyl-tert-butyl ether before being vortex-mixed for 10 seconds. The sample was then centrifuged at 4000 rpm for 3 min and the organic layer was transferred into another sample tube and dried using nitrogen gas at 40^{0}C. After drying, the sample was reconstituted with 100 µL of Acetonitrile: 0.1% Formic acid (50/50, v/v) and vortex-mixed for 5 seconds. An aliquot of 2 µL was injected into the LC-MS/MS system set up with Zorbax Eclipse XDB-C18 column at 30^{0}C (2.1 x 150 mm, 5 µm; Acetonitrile: 0.1% Formic acid (50/50, v/v) was used as the mobile phase). The flow rate and mode of elution was at 0.6 mL/min in isocratic. Total run time was 3.5 minutes. The brand of solvents used were Elite Advanced Materials Sdn Bhd and Fisher Chemicals. The injection volume was 2µL in a single injection. The mass spectrometer was operated in the electrospray ionization and positive mode of ionization. Identification of meloxicam (analyte) and meloxicam-d3 (internal standard) was achieved by comparing settings in multiple reaction monitoring for meloxicam (352.0/115.0) and meloxicam-d3 (355.0/115.0) in human plasma with the standard solution, at a similar retention time. The working range of meloxicam was between 20–2500 ng/mL in human plasma at an estimated retention time of 1.4–2.4 min for meloxicam and meloxicam-d3. The sample concentration was determined using inverse prediction method from a weighted linear regression equation.

Statistical analyses

Descriptive analysis included arithmetic means, geometric means, maximum values, minimum values, standard deviations and coefficient of variation. Analysis of Variance (ANOVA) was performed on all major pharmacokinetic parameters.

Natural log transformed AUC_{0-72} and $C_{max,}$ of Meloxicam were analyzed using a mixed-effect model with sequence, period and treatment as fixed effects and subject within sequence as random effect. Estimates of the adjusted mean differences (Test minus Reference) and corresponding 90% CIs were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference). The acceptance criteria of 90% CI of AUC_{0-t} and C_{max} ratios contained within 80% to 125% is consistent with the WHO acceptance criteria stipulated in page 211 of Annex 6 entitled Multi-source pharmaceutical products: guidelines on registration requirements to establish interchangeability.[12]

RESULTS

Study population

Eighteen Filipino men were enrolled and randomized to receive the study treatment. All eighteen subjects completed the study and received 15 mg dose of each of the two meloxicam formulations separated by a 14-day washout period. Their mean age was 21.5 years (range 18–36), mean weight was 61.4 kg (range 48.5–77.0) and mean BMI was 22.9 kg/m^2 (range 18.0–26.8).

Pharmacokinetics

The summary of pharmacokinetic parameters is shown in Table 1. Total exposures (AUC_{0-72} and AUC_{0-inf}) and C_{max} of meloxicam were similar for both formulations. The geometric means of $AUC_{0-72,}$ AUC_{0-inf} and C_{max} were: 60627.0 and 58256.5 h.ng/ml; 67798.4 and 64788.2 h.ng/ml; and 2072.2 and 2005.3 ng/ml for meloxicam and Mobic®, respectively. Similarity of both formulations is further illustrated in the plasma meloxicam concentration-time curves (Figure 1).

Comparing meloxicam 15 mg tablet with Mobic® 15 mg tablet, the ratios of the log transformed geometric means of the primary endpoints, AUC_{0-72} and C_{max} is shown in Table 2. The limits of the 90% CI for both AUC_{0-72} and C_{max} were within the bioequivalence limits of 80% to 125% (Table 2).

Adverse events

No adverse event occurred. There were no clinically significant deviations in vital signs throughout the whole study period. Repeat hematology and blood chemistry laboratory test results at the last visit remained within normal limits.

DISCUSSION

Meloxicam is a widely prescribed NSAID indicated for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Due to the availability of several formulations, it is important to

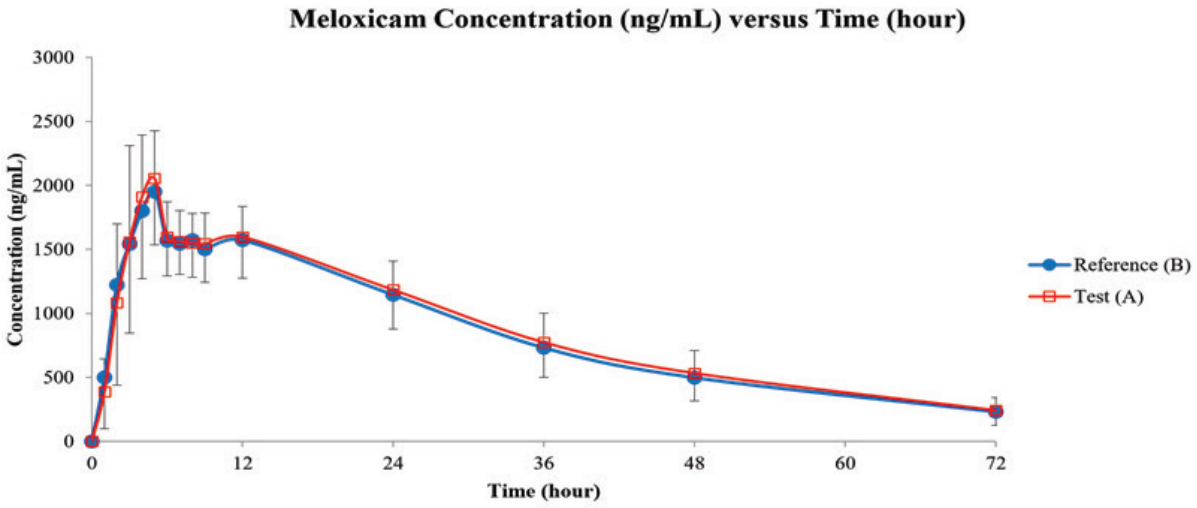

Figure 1. Mean plasma meloxicam concentration-time curve.

Table 1. Summary of pharmacokinetic parameters of plasma meloxicam following oral doses of meloxicam 15 mg tablet formulation and Mobic® tablet

Parameter (Units)	Meloxicam 15 mg Tablet (Test) n=18	Mobic® 15 mg Tablet (Reference) n=18
$AUC_{0\text{-}72\ (h.ng/mL)}$*	60627.0 (20)	58256.5 (25)
$C_{max\ (ng/mL)}$*	2072.2 (18)	2005.3 (19)
$T_{max\ (h)}$†	5.056 ± 1.798	4.667 ± 1.085
$AUC_{0\text{-}inf\ (h.ng/mL)}$*	67798.4 (23)	64788.2 (28)
$T_{1/2\ (h)}$†	20.852 ± 4.187	20.459 ± 3.501
$K_{el\ (h^{-1})}$†	0.03464 ± 0.00766	0.03498 ± 0.00699

**Geometric mean (% CV) – these parameters are analyzed as geometric means in a BE study; †arithmetic mean (SD)*

Table 2. Ratio of the adjusted geometric means and corresponding 90% confidence intervals for meloxicam plasma pharmacokinetic parameters following single oral doses of meloxicam 15 mg tablet formulation and Mobic® tablet

Parameter	Ln Transformed Data					
	Geometric Mean		Ratio %	90% CI	Intra Subject CV (%)	Power (%)
	Meloxicam	Mobic®				
Ln $AUC_{0\text{-}72}$	60627.04	58256.49	104.07	100.26 – 108.03	6.42	100.00
Ln C_{max}	2072.21	2005.33	103.34	96.22 – 110.97	12.30	99.91

CI, Confidence Interval; CV, Coefficient of Variation- ratio of the standard deviation to the mean in percentage

establish bioequivalence, which is a determinant of interchangeability.

Maximum plasma concentration (C_{max})

C_{max} is the maximum plasma drug concentration obtained after oral drug administration. In this study, the maximum plasma concentration (Cmax) was similar for the 15 mg meloxicam tablet and 15 mg Mobic® tablet, as were the terminal elimination half-lives, median time to reach maximal concentrations and elimination rate constants. From a previous meloxicam study in Caucasians under fasted conditions, a single oral dose of a 15 mg capsule achieved a C_{max} value of 928 ng/ml.[9] In another study, also involving healthy Caucasian volunteers, the C_{max} value attained was reported as 0.933 mg/l, which translates to 933 ng/ml.[13] The greater concentrations reached in our study may be explained by CYP2C9 polymorphisms that are also found in Asian populations and are associated with a significant reduction in the metabolism of NSAIDs.[14,15] A study among East Asian populations noted that the CYP2C9*3/*3 genotype

was found to have the greatest decrease in clearance (80%) compared to Caucasian models with the CYP2C9*1/*1 genotype. Other polymorphisms seen in the East Asian subjects showed 15% to 55% decrease in clearance.[16] In a Korean study, a nine-fold lower apparent oral clearance and an eight-fold higher AUC of single-dose meloxicam were observed in CYP2C9*3/*3 individuals.[17] A study among Korean subjects showed that the C_{max} of meloxicam in subjects with *CYP2C9*1/*13* was 1.46 times greater compared to subjects with the *CYP2C9*1/*1* genotype.[18] A Philippine study showed that for CYP2C9*1 and CYP2C9*3, the allele frequencies among Filipinos were similar with East Asians.[19] However, the same study noted that, in general, the frequency of polymorphism, particularly of CYP2C9*2 and CYP2C9*3, are higher for Caucasians than for Asians (including Filipinos), making polymorphism less likely as the explanation for the results observed in this study. However, since the cited studies on Caucasians indicating higher metabolism and clearance and our study among Filipinos indicating lower metabolism and clearance did not determine genetic polymorphism, this could not be confirmed. A more appropriate study with polymorphism determination is needed to confirm this.

Area under curve (AUC)

The AUC represents the total amount of drug that reaches the systemic circulation. The AUC_{0-72} and AUC_{0-inf} values in this study are considerably higher than those seen in German subjects receiving similar dose with AUC_{0-inf} values recorded at 34499.0 and 33784.3 h·ng/ml.[9] Among French subjects, the AUC_{0-inf} values were at 28800h·ng/ml.[13] Since a higher AUC may also correlate with slower metabolism, the discussion on polymorphism in the C_{max} also applies here.

Time of peak plasma concentration (T_{max})

The time of peak plasma concentration (T_{max}) reflects the time to reach the maximum drug concentration. In this study, the median T_{max} values obtained were similar. The values obtained were consistent with prior studies.[9,20] In a study involving healthy Caucasian volunteers, T_{max} of 5 hrs (3-7) and 5 hrs (2-8) were also reported.[9]

Half-life ($t_{1/2}$)

Half-life is the time wherein the drug concentration is reduced to one half of its original concentration in the plasma. In this study, half-lives of test and reference formulations are higher than in Caucasian studies. In a study on 12 healthy Caucasian volunteers, the $t_{1/2}$ reported was 19.3 hrs after a single oral dose of 15 mg capsule.[20] In another study conducted among Caucasian volunteers using same dose, the half-lives reported were 18.29 and 18.94 hours for test and reference, respectively.[9] Since a longer half-life may also correlate with slower metabolism, the discussion on polymorphism in the C_{max} section also applies here.

Comparison of Test and Reference Products

The study showed that the bounds of the 90% confidence intervals for the ratios of the geometric means for the primary endpoints, AUC_{0-72} and C_{max}, were within the accepted bioequivalence limits of 80 to 125%.

The pharmacokinetic parameters obtained demonstrate similarity in the extent and rate of absorption of the two formulations. The two formulations can be considered therapeutic equivalents and can be used interchangeably with no need for gradual dose titration.

Single doses of both formulations were safe and well tolerated in healthy volunteers. It should be noted that the subject number was not sufficient to detect infrequent or rare adverse events. Further, adverse events that may manifest in taking a full course of meloxicam may not manifest after only one or two doses of the drug.

It is a typical assumption in bioequivalence studies that bioequivalence of a product under investigation is predictive of clinical outcomes (i.e., safety and tolerability) with the 90% confidence interval of the ratio of geometric means of the primary pharmacokinetic parameters (AUC and C_{max}) being totally within the bioequivalence limits of 80% to 125%. However, this one-size-fits-all criterion has been challenged and criticized as not taking into consideration factors such as therapeutic window and intra-subject variability in drug response, which may have an impact on both efficacy and safety.[21] Hence, it is prudent for a bioequivalence study to look into safety as a separate parameter, as in any other drug trial. Safety is normally assessed by the presence of adverse events attributable to the drug and tolerability of these events.

CONCLUSIONS

Based on the results of this bioequivalence study, meloxicam 15 mg tablet of Pascual Laboratories, Inc. and the reference, Mobic® tablet (15 mg) by Boehringer Ingelheim, are bioequivalent and thus, considered as therapeutically equivalent. Single doses of meloxicam 15 mg tablets were safe and well tolerated. Thus, the two drug formulations may be used interchangeably with no need for gradual dose titration.

Statement of Authorship

All authors participated in the data collection and analysis and approved the final version submitted.

Author Disclosure

Dr. Rita Grace Alvero, Clinical Director and Dr. Josefino Alvero, President and COO of Pharmalytics Corporation reports personal fees from Pascual Laboratories, Inc, during the conduct of the study, and Dr. Geraldo Balaccua, Medical and Regulatory Affairs Director of Pascual Laboratories, Inc reports personal fees from Pascual Laboratories, Inc., outside the submitted work.

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