Bioequivalence of two Oral Formulations of Etoricoxib 60 mg Tablets in Healthy Mexican Adults

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**ABSTRACT**

Etoricoxib is a potent selective Cyclo-oxygenase 2 inhibitor with anti-inflammatory and analgesic properties. Here we investigate the bioavailability and the bioequivalence of a test formulation containing 60 mg of etoricoxib with respect to the corresponding reference drug formulation, which was administered as a tablet. A single-dose randomized, open-label, two-sequence, two-period crossover design under fasting conditions with a 12-day washout interval between the two periods was used.

Samples were drawn at baseline and then at 0.25, 0.5, 0.75, 1.00, 1.25, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours after administration.

The 90% CIs for etoricoxib Cmax and truncated AUC0–72 were 99.55% to 119.33%, and 95.97% to 103.06%, respectively. The 90% CIs of the geometric mean ratios of the two parameters fell within the predetermined range of 80% to 125%. Therefore, these results indicate that the bioequivalence criteria were satisfied.

**Keywords:** Etoricoxib; Bioavailability; Bioequivalence

**INTRODUCTION**

Etoricoxib is a potent selective Cyclo-oxygenase 2 inhibitor with anti-inflammatory and analgesic properties. The therapeutic indications of etoricoxib in different countries include treatment for the signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis, chronic low back pain, acute pain, chronic musculoskeletal pain and primary dysmenorrhoea [1-4].

The pharmacokinetics of etoricoxib appears to be linear over a dose range from 5 to 120 mg [5]; its absolute bioavailability has been estimated to be near to 100% [1,6].

The elimination half-life of etoricoxib has been estimated (harmonic mean) to be 24.8 hours [7]. Etoricoxib elimination occurred primarily through metabolism followed by renal excretion [4].

*In vitro* studies in human liver microsomes have indicated that etoricoxib is metabolized via oxidative pathways by cytochromes P450 [1,7].

The single-dose oral pharmacokinetics of etoricoxib are independent of food because the extent of absorption remained intact. Thus, etoricoxib may be taken with or without food [4].

Etoricoxib is available at the strengths of 30, 60, 90 and 120 mg [4]. The sponsor of this study (Laboratorios Liomont, S.A. de C.V., Mexico City, Mexico) wished to obtain the marketing authorization for etoricoxib 60 mg in tablet formulation in Mexico.

Therefore, the aim of this study was to assess the bioavailability and the bioequivalence of a test formulation containing 60 mg of etoricoxib compared with the corresponding reference drug formulation.

A literature survey using PubMed, MEDLINE and Google Scholar data through March of 2018 yielded no matches for the following terms: etoricoxib, 60 mg, bioequivalence, bioavailability, pharmacokinetics, tablets, Mexico, Mexican and population.

**METHODS**

**Formulations**

The test formulation consisted of Doscoxel tablets containing 60 mg of etoricoxib, manufactured by Laboratorios Liomont, S.A. de C.V. (Mexico). The lot number was 298G0039, and the expiration date was November 30, 2018. The reference formulation consisted of Arcoxia tablets containing 60 mg of etoricoxib, manufactured by Frosst Iberica; S.A. (Spain) and distributed by Schering-Plough, S. A. de C. V. (Mexico). The lot number was L045340, and the expiration date was May 31, 2017.

**Ethical considerations**

An independent ethics and research committee (Committee of Ethics in Research and Committee of Investigation of Arete and Projects and Administration) reviewed and approved the study protocol (ETR-03-LIO) and the informed-consent documents on June 29, 2016. This investigation was authorized by the Federal Commission for Protection against Sanitary Risks (Comision Federal para la Protection contra Riesgos Sanitarios (COFEPRIS)) on August 9, 2016.

The study was conducted according to the Declaration of Helsinki (and its amendments) and the International Conference on Harmonization for Good Clinical Practice Guideline. The principal investigator informed the participants of the anticipated risks and potential discomfort associated with the study drug, the procedures and the duration of the study. All of the subjects gave written informed consent prior to the initiation of the study. The clinical stage of the study was conducted in May of 2017.

**Subjects**

Healthy Mexican adults of both genders with ages between 18 and 55 years were considered to be eligible for this study. The health of each candidate was evaluated. This evaluation included an interview and a physical examination of vital signs, blood pressure, heart rate, temperature, 12-lead electrocardiogram and chest radiography. Furthermore, laboratory tests (hematology and blood chemistry, urinalysis, and tests for alcohol, drug-abuse and a pregnancy test for women) and serological tests (hepatitis B and C, as well as HIV antibodies) were conducted.

**Study design and Drug administration**

A single-dose randomized, open-label, two-sequence, two-period crossover design under fasting conditions with a 12-day washout interval between the two periods was used. In addition, the design was regarded as truncated (That is, the blood sampling collection period was restricted to 72 hours because of the long elimination half-life of etoricoxib of roughly 24 hours).

The subjects were admitted to a clinical unit (Investigacion Farmacologica y Biofarmaceutica) on the day before the drug administration. They were randomly assigned to one of the two
The subjects were administered a single tablet of the test or the reference formulation with 250 mL of water after fasting for at least 10 hours. Blood samples (7 mL) were drawn from each subject using an indwelling cannula. These samples were placed into heparinized (sodium heparin) tubes. The samples were obtained at baseline (predose) and then at 0.25, 0.5, 0.75, 1.00, 1.25, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours after administration. The subjects then returned to the clinical unit after the washout period to receive the alternative formulation.

The blood samples were centrifuged at 4500 rpm for 5 minutes. The resulting plasma samples were stored at -70°C ± 10°C until being transported to the analytical unit (Biokinetics) where they were stored at -75°C ± 5°C until analysis. The subjects’ diet consisted of standardized meals (breakfast, lunch and dinner) which were provided at 4, 8 and 12 hours after drug administration.

**Determination of Etoricoxib plasma concentrations**

**Chemicals:** Etoricoxib (batch: 20-SSR-57-1), the reference substance was obtained from the Toronto Research Chemicals Inc (Toronto, Canada) and sildenafil citrate (internal standard, batch: 00139) was obtained from MAPRIMED (Buenos Aires, Argentina). The water was obtained from a Barnstead water purification system (Thermofisher Scientific, OH, USA) and the solvents were HPLC grade (Avantor Performance Materials, LLC, PA, USA and Honeywell International Inc. MI, USA) and all reagents were analytical grade (Sigma-Aldrich, Inc. Missouri, USA).

**Method and sample preparation:** The etoricoxib plasma concentrations were determined using a HPLC method coupled with ultraviolet spectroscopy; this method was developed and validated by Biokinetics personnel in Mexico City, Mexico.

A sample consisting of 500 μL of plasma and 10 μL of internal standard (sildenafil, 250 μg/mL) was extracted with 1000 μL of a solvent mixture consisting of ethyl acetate and tert-butyl methyl ether (90:10 v/v). These components were vortexed for one minute and centrifuged at 8000 rpm for 5 minutes at 20°C. The organic phase (800 μL) was separated and placed into a test tube where it was subjected to evaporation to dryness under a nitrogen current, at 50°C for 4 minutes. The residue was reconstituted with a mixture of 100 μL consisting of water and acetonitrile (50:50 v/v) and 20 μL was injected into the chromatographic system (HPLC, Agilent Technologies, model 1200, Palo Alto, CA, California).

**Chromatographic conditions:** The analytical column was a Zorbax® SB-C8 (12.5 × 4.6-mm internal-diameter column of 5-μm particle size (Agilent Technologies)) and the precolumn was a Zorbax® SB-C18 (150 × 4.6-mm internal-diameter column of 5-μm particle size (Agilent Technologies))). Etoricoxib and the internal standard were eluted with a mobile phase consisting of a mixture (55:45 v/v) of aqueous ammonium acetate (10 mM, pH = 5.5 ± 0.1) and acetonitrile.

The column temperature was 25°C and both analytes were detected by using an ultraviolet detector (Agilent Technologies, model G1314B) at a wavelength of 284 nm. The flow of the mobile phase was 1 mL/minute. The typical retention times for etoricoxib and the internal standard were 4.9 and 5.9 minutes, respectively. The peak areas were measured to calculate the peak area ratio of etoricoxib with respect to that of the internal standard. We then calculated the concentration.

**Method validation:** We validated the analytical method in accordance with Mexican and international guidelines [8,9]. Analysis of blank human plasma samples from six different subjects, blank human (hemolyzed and lipemic) plasma samples, as well as anticoagulants (lithium and sodium heparin), xanthines (caffeine and theobromine), and other drug substances commonly used as analogues (acetylsalicylic acid, diclofenac, paracetamol, ibuprofen and naproxen) were used to test the selectivity of the method. No interferences were observed in the resulting chromatograms.

The calibration curve consisted of the following etoricoxib concentrations: 10, 20, 600, 1000, 1800, 2400 and 2800 ng/mL. (i.e., the range of the method was 10-2800 ng/mL, and the lower limit of quantification (LLOQ) of 10 ng/mL). The method was linear over this range of concentrations, and the coefficient of determination was 0.99 (average from 4 calibration curves). The intra-assay %CV and accuracy (relative error) of etoricoxib were 1.85% to 3.31% and 1.85% to 9.68%, respectively; and the inter-assay %CV and accuracy were 4.46% to 6.36% and -14.60% to 9.68%, respectively.

Etoricoxib was found to be stable in plasma for at least 24 hours at room temperature (25°C), after three freeze-thaw cycles and after 16 weeks at −75 ± 5°C. We also tested sample dilution to account for etoricoxib concentrations beyond the upper bound of the calibration curve’s range. We prepared quality-control samples at three different concentration levels (designated as low (30 ng/mL), medium (1400 ng/mL) and high (2100 ng/mL) of etoricoxib independent of the calibration curve. The acceptance criteria for the approval of the analytical runs and the quality control samples, as well as the criteria for performing sample reanalysis, were consistent with Mexican and international guidelines.

**Tolerability:** The subjects were interviewed by the principal investigator and/or the study coordinator to determine the occurrence of Adverse Events (AEs) during the study and at the end of the clinical stage of the study. The subjects were asked to spontaneously report any AEs to the principal investigator at any time over the entire duration of the study, including washout period. Adverse events that were life-threatening or led to death, hospitalization, disability, and/or medical intervention to prevent permanent impairment or damage were considered to be serious.

**Pharmacokinetic and statistical analyses:** The sample size calculation [10] was based on the within-subject variability of etoricoxib Cmax with a %CV of 27.67% estimated from data of Shoag et al. [11]. This calculation, performed using the following values: 1 - β = 0.8, α = 0.05, expected ratio (μT / μR) = 0.95 and an equivalence range of 80% to 125%, yielded a sample size of 34 subjects. Therefore, we planned to recruit 36 subjects to account for potential dropouts.

We directly obtained Cmax and Tmax values from the plasma concentration–time curves. Because of the long elimination half-life of etoricoxib, the truncated area under the plasma concentration–time curve from baseline (time 0) to 72 hours (AUC0→72) was used to assess the extent of absorption [12]. From, the terminal log-decay phase, the elimination rate constant (k) was estimated using linear regression, and the t1/2 was estimated using the following equation:

\[ t_{1/2} = \ln(2)/k \]

where \( \ln \) is the natural logarithm.

To assess the bioequivalence between the test and reference formulations, Cmax and the truncated AUC0–72 were considered to be primary variables. Using log-transformed data for these parameters, ANOVA for a 2 x 2 crossover design, was carried out at the significance level of 5% (α = 0.05).
Table 1: Demographic characteristics of subjects.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of recruited subjects (female/male)</td>
<td>36 (20/16)</td>
</tr>
<tr>
<td>Age, mean (SD), range, years</td>
<td>34 (9), 18-54</td>
</tr>
<tr>
<td>Weight, mean (SD), range, kg</td>
<td>62.7 (10.1), 41.0-89.0</td>
</tr>
<tr>
<td>Height, mean (SD), range, m</td>
<td>1.62 (0.09), 1.48-1.85</td>
</tr>
<tr>
<td>BMI, mean (SD), range, kg/m²</td>
<td>23.71 (2.63), 18.59-26.93</td>
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BMI = Body Mass Index
SD = Standard Deviation
formulation with the reference formulation in Mexican patient groups. We expect that the findings of this study may serve as a reference for future controlled studies of etoricoxib in a Hispanic population.

CONCLUSION

This study, which included healthy, fasting Mexican adult subjects, showed that the test formulation of etoricoxib 60 mg met the Mexican regulatory requirements to assume bioequivalence based on the rate and extent of absorption. Both formulations were well tolerated.

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