Brief Report

Bioavailability of Two Sublingual Formulations of Ketorolac Tromethamine 30 mg: A Randomized, Open-Label, Single-Dose, Two-Period Crossover Comparison in Healthy Mexican Adult Volunteers

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ABSTRACT

Background: Ketorolac tromethamine (ie, ketorolac) is an NSAID that appears to have several mechanisms of action, including inhibition of prostaglandin synthesis, modulatory effect on opioid receptors, and nitric oxide synthesis. Ketorolac is used in the treatment of pain. There are various generic formulations of sublingual ketorolac available in Mexico. However, a literature search did not identify published data concerning the bioavailability of these formulations in the Mexican population.

Objective: The aim of this study was to compare the bioavailability of 2 sublingual formulations of ketorolac 30-mg tablets in healthy Mexican adult volunteers.

Methods: This was a randomized-sequence, open-label, single-dose, 2-period crossover (2 dosing periods × 2 treatments) study comparing the bioavailability of two 30-mg sublingual tablet formulations of ketorolac. Healthy Mexican adult (aged, 18–55 years) men and women were eligible for inclusion. Subjects were randomly assigned in a 1:1 ratio to receive a single dose of the test formulation or the reference formulation. After a 12-hour overnight fast, subjects received a single dose of the corresponding formulation. There was a 7-day washout period between administration periods. Plasma samples were obtained over a 24-hour period after administration. Plasma ketorolac concentrations were analyzed by high-performance liquid chromatography for analysis of pharmacokinetic properties, including C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$. Blood samples were drawn immediately after sublingual placement of the drug and at 10, 20, 30, 40, 50, 60, 75, and 90 minutes and 2, 4, 6, 8, 10, 12, and 24 hours after dosing. The formulations were considered bioequivalent if the geometric mean ratios of C_{max} and AUC were within the predetermined range of 80% to 125% and if P for the 90% CIs was <0.05. Tolerability was assessed by vital sign monitoring, laboratory analysis results, and subject interviews.

Results: A total of 27 subjects (18 women, 9 men; mean [SD] age, 27 [9] years [range, 18–47 years]; weight, 61 [8] kg [48–79 kg]; height, 163 [8] cm [150–180 cm]) were enrolled and completed the study. Fourteen subjects received the test formulation first. No period or sequence effect was observed. The 90% CIs for the corresponding differences in natural log C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ were 95.94% to 114.66%, 98.34% to 105.90%, and 99.25% to 108.36%, respectively (all, $P < 0.05$), meeting the predetermined criteria for bioequivalence. Sixteen subjects experienced a total of 20 adverse events (AEs) during the study. None of the AEs were considered serious. One AE (nausea) appeared to be related to use of the reference formulation.

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Conclusions: In this small study in 27 healthy Mexican adult volunteers, the test formulation of a single, 30-mg sublingual tablet of ketorolac appeared to be bioequivalent to the reference formulation based on the rate and extent of absorption. Both formulations were well tolerated. (*Clin Ther.* 2008;30:1667–1674) © 2008 Excerpta Medica Inc.

Key words: ketorolac, ketorolac tromethamine, bioequivalence, bioavailability, pharmacokinetic, HPLC.

INTRODUCTION

Ketorolac tromethamine is an NSAID used in the treatment of moderately severe, acute pain that requires analgesia at the opioid level.[1] Ketorolac, like other NSAIDs, appears to inhibit prostaglandin synthesis,[2] both peripherally[3] and spinally.[4] The mechanisms by which ketorolac may exert a central effect are unclear but may include a modulatory effect on opioid receptors or alterations to opioid pharmacokinetics.[5] Ketorolac does not appear to directly activate opioid receptors, since it has been reported that it does not bind to μ-, κ-, or δ-opioid receptors.[6] The analgesic effects produced by the μ receptor agonist morphine and the κ receptor agonist ketocyclazocine are antagonized by naloxone, whereas that induced by ketorolac was not diminished by either naloxone[7] or quadazocine.[8] Alternatively, ketorolac may cause the release of the endogenous opioid.[9] Because ketorolac has not been associated with respiratory depression or tolerance,[1] the adverse-events (AEs) profile of ketorolac is considered more favorable than that of opioids.[10] However, ketorolac has been associated with peptic ulcer, gastrointestinal bleeding, and perforation.[11] Administration of the nitric oxide synthesis inhibitor NG-nitro-L-arginine methyl ester reduced the antinociceptive effect of ketorolac in the pain-induced functional impairment in a rat model.[12] This finding led the authors to conclude that local nitric oxide synthesis may be involved in the analgesic effect of ketorolac.[12] There is evidence suggesting that ketorolac may interact with the cannabinoid receptor.[13] It has also been reported that ketorolac was associated with mitochondrial calcium release, and this activity may be involved in the production of its analgesic effect.[14]

Although several sublingual generic formulations of ketorolac are available in Mexico, a search of the literature using the MEDLINE database (years: 1990–2007; terms: *bioequivalence*, *bioavailability*, *pharmacokinetics*, *Mexico*, and *ketorolac*) did not identify published data concerning the bioavailability of each formulation in the Mexican population. Sublingual administration may have several advantages, such as improved bioavailability[15] and ease of administration, especially for patients who have difficulty swallowing tablets.

The aim of the present study was to compare the bioavailability of 2 sublingual formulations of ketorolac used in Mexico—a test formulation* and a reference formulation†—in healthy Mexican adult volunteers.

SUBJECTS AND METHODS

Inclusion/Exclusion Criteria

Healthy Mexican adult men and women aged 18 to 55 years were eligible for inclusion. Subjects were recruited from an outpatient records retrieval database within the Pharmacology Research Unit at Medica Sur Hospital, Mexico City, Mexico. All subjects provided written informed consent prior to the commencement of the study. Thereafter, the subjects' medical histories were documented and a physical examination was conducted. Supine systolic and diastolic blood pressures were recorded. Inclusion eligibility was also based on the successful completion of a clinical health evaluation that consisted of a personal interview, a complete physical examination (blood pressure, pulse, weight, height, temperature, respiratory rate), and diagnostic testing that included a 12-lead electrocardiogram and chest radiograph. Laboratory testing included a complete blood cell count, metabolic and hepatic tests (alanine aminotransferase [reference range, 8–44 U/L] and aspartate aminotransferase [13–34 U/L]), urinalysis, pregnancy test (for female subjects), serologic tests for glucose (72–100 mg/dL), blood urea nitrogren (5.7–23.1 mg/dL), creatinine (0.6–1.3 mg/dL), as well as hepatitis B and HIV antibodies. Volunteers were excluded if laboratory values were significantly above or below the reference range and/or if all tests had not been performed. Testing was performed by the laboratory at Medica Sur Hospital, which has been accredited by the Mexican government.

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Study Design and Drug Administration

This was a randomized-sequence, open-label, single-dose, 2-period crossover (2 dosing periods × 2 treatments) study comparing the bioavailability of two 30-mg sublingual tablet formulations of ketorolac. The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments,[16] the International Conference on Harmonisation Guideline for Good Clinical Practice,[17] General Law on Health Care for Mexico,[18] applicable local sanitary regulations, and established international standards.[17,19] The study protocol and the informed-consent form were approved by the Ethics and Research Committee at Medica Sur Hospital and by the Federal Commission for the Protection Against Sanitary Risks (COFEPRIS) Ministry of Health of the United Mexican States.[18]

Subjects arrived at the clinical unit/site the day before the commencement of the study and were randomized in a 1:1 ratio using a table of random numbers to receive the test formulation followed by the reference formulation, or vice versa. To obtain accurate baseline plasma measurements, subjects underwent a 12-hour overnight fast. Blood samples drawn using an 18-G × 1.16-in (1.3 × 30 mm) or 20-G × 1.16-in (1.1 × 30 mm) indwelling angiocatheter (BD-InSyte, Becton, Dickinson and Company, Saõ Paulo, Brazil), which was inserted into the subjects' forearm vein and collected into a 7.5-mL heparinized tube (S-Monovette, Sarstedt AG & Co., Nümbrecht, Germany). Before collection of each blood sample, 1 mL of blood was drawn from the angiocatheter and discarded. To ensure patency, 0.5 mL of lithium heparin (25 IU/mL) was injected into the angiocatheter after each blood sample was drawn. Subjects received a single 30-mg tablet of either the test or the reference formulation, administered sublingually over a period of 5 minutes. After the 5-minute period, any remaining tablet was swallowed. Blood samples were drawn immediately after the tablet was placed under the tongue (time 0) and at 10, 20, 30, 40, 50, 60, 75, and 90 minutes and 2, 4, 6, 8, 10, 12, and 24 hours after drug administration. Plasma was obtained by centrifugation (1000*g* for 15 minutes at room temperature [25°C]) and stored frozen at −75°C ± 5°C until analyzed using high-performance liquid chromatography (HPLC). After a 7-day washout period, subjects returned to the clinical unit, where the alternative formulation was administered and samples were drawn and analyzed as in the first treatment period.

Plasma Ketorolac Concentration Measurements

Plasma ketorolac concentrations were determined using an HPLC method developed by personnel at Fundación Liomont A.C., Mexico City, Mexico, in which naproxen was used as the internal standard. The method included: 0.5 mL of plasma, 0.01 mL of internal standard (naproxen 1500 μg/mL), and 0.5 mL of zinc sulfate 0.014 M. These constituents were mixed together in a 2.0-mL conical tube (Sarstedt AG & Co.) for 1 minute. The tube was cooled in a freezer (−75 ± 5°C) for 1.5 minutes and then centrifuged at 1440*g* for 12 minutes at room temperature (25°C). The supernatant was separated and injected into the chromatographic system (Model 1100, Agilent Technologies, Palo Alto, California). Ketorolac concentration was determined with a 15-cm × 4.6-mm internal-diameter column of 5-μm particle size (Zorbax Eclipse XDB-C18, Agilent Technologies) and eluted with a mobile phase consisting of a mixture (56:44 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 1.0 mL/min and the ketorolac was detected by a UV detector (Agilent Technologies) set at a 313-nm wavelength. Typical retention times for ketorolac and internal standard were 3.9 and 6.9 minutes, respectively. The ketorolac peak area was used for quantification. Under these conditions, the method was linear in the range of 0.1 to 5 μg/mL (0.1, 0.3, 0.6, 1.5, 3, and 5 μg/mL), with lower limits of quantification and detection of 0.1 and 0.03 μg/mL, respectively. Accuracy was between 98.66% and 103.73%; the relative SD of the method was always <4%. This method was considered suitable by the study investigators for the pharmacokinetic study of ketorolac.

Tolerability

Tolerability was determined by clinical assessment, vital sign monitoring (blood pressure, heart rate, and body temperature) at baseline and 8 and 24 hours after drug administration, as well as laboratory results.

AEs were recorded by way of personal interview (investigators interviewed subjects in accordance with the case-report form) at the beginning and end of each period. In addition, the subjects were required to spontaneously report any AE to the investigators at any time during the study, including the washout period.

AEs that were life-threatening, led to death, hospitalization, disability, or medical intervention to pre-

vent permanent impairment or damage were considered serious.

Pharmacokinetic and Statistical Analyses

Individual plasma concentration–time curves were constructed; C_{max} and T_{max} were obtained directly from these curves. AUC_{0-24} was calculated using the trapezoidal rule.[19] From the terminal log-decay phase, the elimination rate constant (k_e) was estimated using linear regression, and $t_{1/2}$ was estimated using the following equation[20]:

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

where *ln* was defined as the natural logarithm. Extrapolation of AUC from baseline to infinity ($AUC_{0-\infty}$) was calculated as follows[20]:

$$AUC_{0-\infty} = AUC_{0-24} + (C_{24}/k_e),$$

where C_{24} was defined as the concentration at 24 hours.

Bioavailability was defined in accordance with the in vivo bioequivalence guidance criteria established by the US Food and Drug Administration,[19] which states that it is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action of the formulations tested. An analysis of variance (ANOVA) for a 2 × 2 crossover design in ln-transformed C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ was carried out to determine bioavailability. The 90% CIs for the corresponding differences in C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ were calculated, and ANOVA was performed using the *F* ratio. Probability of exceeding the limits of acceptance (80%–125%) was obtained by two 1-sided *t* tests described by Schuirmann.[21] The 2 formulations were considered bioequivalent if the geometric mean ratios of the C_{max} and AUC were within the predetermined range of 80% to 125% and if *P* for the 90% CIs was <0.05.[19] All pharmacokinetic and statistical analyses were performed using WinNonlin version 5 (Pharsight Corporation, Mountain View, California).

RESULTS

A total of 27 subjects (18 women, 9 men; mean [SD] age, 27 [9] years [range, 18–47 years]; weight, 61 [8] kg [48–79 kg]; height, 163 [8] cm [150–180 cm] were included in and completed the study. Fourteen subjects received the test formulation first.

Pharmacokinetic Properties

Mean plasma concentration–time curves of the ketorolac formulations are shown in the **figure**, and the pharmacokinetic properties (C_{max}, T_{max}, $t_{1/2}$, AUC_{0-24}, and $AUC_{0-\infty}$) are summarized in **Table I**. The C_{max} values of ketorolac were similar in the test and reference formulations (3.61 vs 3.44 μg/mL, respectively). In addition, T_{max} values were similar (0.66 hour for test formulation and 0.94 hour for reference formulation; similar considering SDs), as well as geometric mean ratios (ranging from 102.05% to 104.88%; **Table II**). No period or sequence effects were detected for the pharmacokinetic properties in the ANOVA. In addition, there was no evidence of weight-related differences in individual C_{max} and AUC values. Estimated C_{max} values for the 2 formulations were 3.61 (test formulation) and 3.44 μg/mL (reference formulation), and AUC_{0-24} values were 12.17 and 11.80 $\mu g/mL \cdot h^{-1}$, respectively. **Table II** shows the 90% CIs for the ln-transformed values of C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ and the probability of exceeding the limits of acceptance (Schuirmann's 1-sided *t* tests, and the power of the test).[18–23] The 90% CIs for the corresponding ratios of C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ were within the 80% to 125% range. All *P* values were <0.05.

Tolerability

Sixteen subjects experienced a total of 20 AEs during the study (**Table III**). However, none were considered serious in the opinion of the investigators. One AE (nausea) appeared to be related to use of the reference formulation. Three AEs required orally administered medication: rhinopharyngitis (ibuprofen), headache (paracetamol), and otalgia (ibuprofen). The rest of the AEs resolved spontaneously.

One volunteer was not considered for the evaluation of bioequivalence because interference with the internal standard signal was detected in the predose sample (study period 1). However, this volunteer was included in the tolerability assessment.

DISCUSSION

The results of the present study suggest that the 2 ketorolac formulations were comparable in terms of their pharmacokinetic characteristics in these healthy volunteers. The C_{max} values of ketorolac were similar

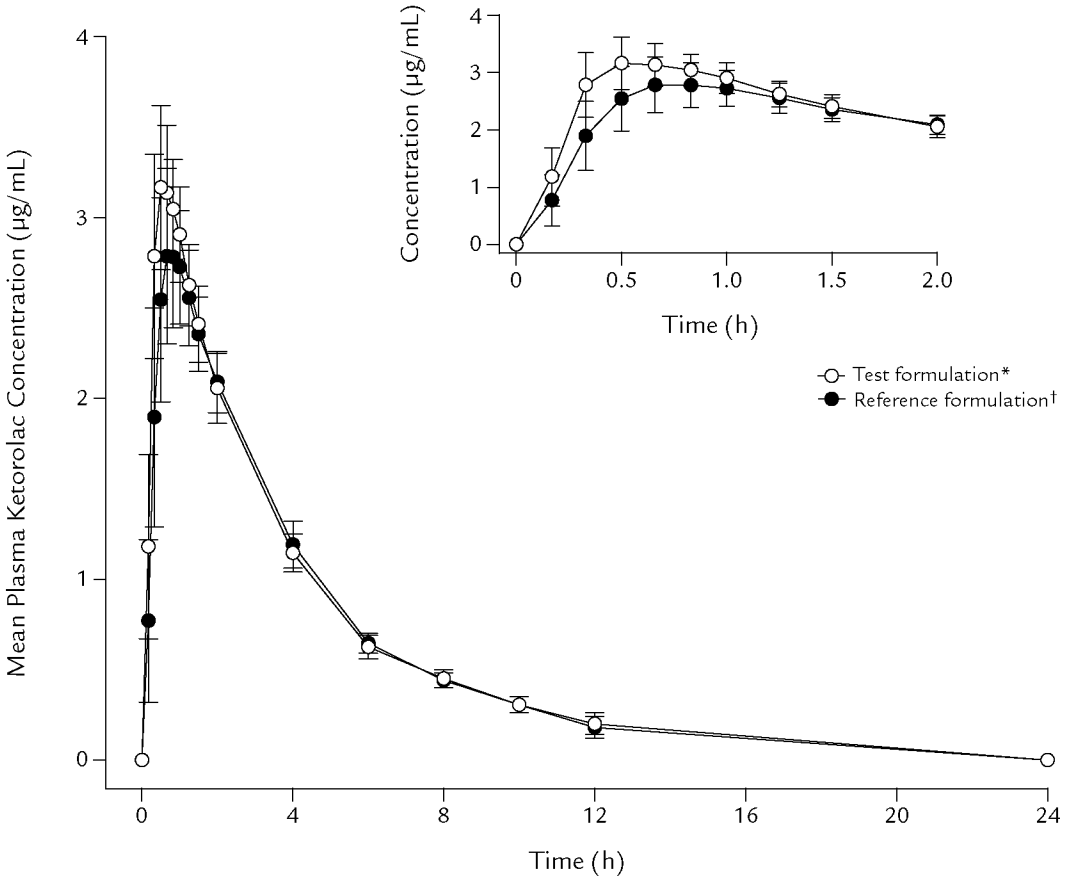

Figure. Mean (95% CI) plasma concentration–time curves of the sublingual ketorolac 30-mg test* and reference† formulations over 24 hours in healthy Mexican volunteers (N = 26). *Trademark: Supradol® (Laboratorios Liomont S.A. de C.V., Mexico City, Mexico); †Trademark: Dolac® (Syntex S.A. de C.V., Mexico City, Mexico).

in the test and reference formulations. In addition, T_{max} values were similar for the reference formulation as well as geometric mean ratios. These findings suggest that the 2 formulations had similar absorption patterns in this small study population. Considering that the pharmacokinetic properties of ketorolac were similar between the 2 formulations, we suggest that their rates and extents of absorption are comparable.

The Schuirmann 1-sided *t* tests (probability of exceeding limits of acceptance) found all *P* values <0.05. Thus, the hypothesis that the estimated parameters exceeded limits of acceptance was rejected.

A poststudy calculation based on the ANOVA error data (C_{max} intrasubject CV [CV intra], 18.69%; AUC_{0-24} CV intra, 7.85%; and $AUC_{0-\infty}$ CV intra, 10.12%) revealed that sample sizes of 14, 4, and 4 subjects, respectively, were sufficient to show differences of 20% between the 2 formulations for these pharmacokinetic properties. Therefore, the 27 subjects included in this study were indeed enough for the purposes of this study (power derived from ANOVA >0.8). Type I and II errors would not exceed 5% and 20%, respectively.

None of the 20 AEs reported were serious. The most frequent was headache (n = 2) but was unrelated to the drug. Nausea was present in 1 subject, and it appeared to be related to the drug (reference formulation).

Because only 1 dose of each formulation was administered during each treatment period, subjects were under medical surveillance during the entire du-

Table I. Pharmacokinetic parameters of sublingual ketorolac 30 mg (test* or reference† formulation) after a single dose in healthy Mexican adult volunteers (N = 26).‡ Values are mean (SD).

Parameter	Test	Reference
C_{max}, μg/mL	3.61 (0.90)	3.44 (1.02)
T_{max}, h	0.66 (0.38)	0.94 (0.81)
$t_{1/2}$, h	4.27 (1.76)	3.71 (1.08)
AUC_{0-24}, μg/mL · h^{-1}	12.17 (2.60)	11.80 (2.20)
$AUC_{0-\infty}$, μg/mL · h^{-1}	13.92 (3.03)	13.27 (2.29)

AUC_{0-24} = AUC from time 0 (baseline) to 24 hours; $AUC_{0-\infty}$ = AUC from baseline to infinity.
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‡No significant between-treatment differences were found.

ration of the 2 periods in the clinical unit, and the duration of the washout period was only 7 days, potential recall bias of AEs in this study was not likely.

Limitations

As with any clinical trial, the current study had some limitations that should be considered. This was an open-label study, so it might not have objectively addressed the safety profiles of the formulations tested. The data were obtained from healthy subjects who were administered a single dose; the pharmacokinetic characteristics of ketorolac might differ in target populations. Because of the limited data, we were unable to predict the response of the drug at any time following alternative doses and/or administration intervals with the present data set. Further studies are needed to determine whether the test formulation has similar or increased efficacy and/or tolerability compared with the reference formulation in Mexican patient groups, considering the comparable pharmacokinetic profiles of the 2 formulations.

The results of this study, obtained from a sample of healthy Mexican adult volunteers, might serve as a reference for future controlled studies of ketorolac in the Hispanic population.

CONCLUSIONS

In this small study in healthy Mexican adult subjects, a single 30-mg dose of the test formulation of sublingually administered ketorolac appeared to be bioequivalent to the reference formulation, based on the rate and extent of absorption. Both formulations were well tolerated.

Table II. Comparison of 90% CIs of natural logarithm (ln)-transformed parameters (C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$), the probability of exceeding the limits of acceptance, and power test results for ketorolac 30 mg, sublingually administered in both test* and reference† formulations to healthy Mexican adult volunteers (N = 26).

Parameter	Ratio, % Reference	90% CI	Probability of Exceeding Limits of Acceptance: $P < 80\%$	Probability of Exceeding Limits of Acceptance: $P > 125\%$	Power
ln C_{max}	104.88	95.94–114.66	<0.001	<0.001	0.99
ln AUC_{0-24}	102.05	98.34–105.90	<0.001	<0.001	1.00
ln $AUC_{0-\infty}$	103.71	99.25–108.36	<0.001	<0.001	1.00

AUC_{0-24} = AUC from time 0 (baseline) to 24 hours; $AUC_{0-\infty}$ = AUC from baseline to infinity.
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Table III. Adverse events (AEs)* after administration of the test† or reference‡ formulation of sublingual ketorolac 30-mg tablets in healthy Mexican adult volunteers (N = 27).

Subject No.	AE	Duration, d	Relation to Study Drug Formulation	Action
2	Left wrist paresthesia	8	Unrelated/reference	Observation
4	Neck sprain	8	Unrelated/reference	Observation
5	Left wrist paresthesia	7	Unrelated/test	Observation
6	Left hand pain	7	Unrelated/reference	Observation
8	Local postvenipuncture ecchymosis (right arm)	13	Unrelated/test	Observation
9	Dizziness	1	Unrelated/test	Observation
	Pharyngitis§	4	Unrelated/test	Observation
16	Local postvenipuncture ecchymosis (right arm)	11	Unrelated/test	Observation
	Right arm pain	8	Unrelated/test	Observation
17	Cough	5	Unrelated/reference	Observation
18	Local postvenipuncture ecchymosis (left arm)	14	Unrelated/test	Observation
19	Nausea	<1	Related/reference	Observation
20	Abdominal pain	<1	Unrelated/test	Observation
	Abdominal pain	<1	Unrelated/test	Observation
	Abdominal pain	<1	Unrelated/test	Observation
22	Rhinopharyngitis§	4	Unrelated/reference	Medication (ibuprofen)
23	Headache	<1	Unrelated/reference	Medication (paracetamol)
24	Headache	<1	Unrelated/test	Observation
26	Otalgia	7	Unrelated/reference	Medication (ibuprofen)
27	Menstrual cramps	3	Unrelated/test	Observation

*All AEs were considered mild.
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§AEs reported during the washout period. All others were reported within 24 hours after administration of either formulation.

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