



The Bioequivalence Study of Two Dexketoprofen 25 mg Film-Coated Tablet Formulations in Healthy Males Under Fasting Conditions

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ABSTRACT

Objectives: Dexketoprofen is a non-steroidal analgesic/anti-inflammatory drug and its trometamol salt is extensively preferred in mild or moderate pain due to its rapid onset of relief. A new formulation of 36.9 mg of dexketoprofen trometamol (equivalent to 25 mg dexketoprofen) tablet has been developed and its bioequivalence to the reference product was proven.

Materials and Methods: An open-label, single-dose, randomized, two-period, and cross-over bioequivalence study was conducted with healthy males under fasting conditions for two different tablet formulations of 25 mg dexketoprofen. To prove the bioequivalence of the test product with the reference product, a comparison study has been performed in compliance with regulations in force under Good Clinical Practice principles. A single-center clinical study was run and blood samples of the participants were withdrawn at specified time points, before and after dosing, to measure the plasma concentrations of dexketoprofen trometamol. A validated analytical method has been developed using an liquid chromatography with tandem mass spectrometry. Instrument to assess the plasma concentrations of the test and reference products.

Results: Forty-seven volunteers completed clinical phase of the study. For the test and reference products, the mean \pm standard deviations (SD) of C_{max} were found 2543.82 ± 655.42 ng/mL and 2539.11 ± 662.57 ng/mL, and the mean \pm SD of area under the curve (AUC) from time 0 to the last measurable concentration ($AUC_{0-tlast}$) were found 3483.49 ± 574.42 h.ng/mL and 3560.75 ± 661.83 h.ng/mL, respectively. The primary target variables data demonstrate the bioequivalence of test and reference products with regard to 90% confidence interval for C_{max} of 92.45-108.53% and for $AUC_{0-tlast}$ of 95.57-100.87%. The geometric mean ratios were found as 100.16% and 98.18% for C_{max} and $AUC_{0-tlast}$, respectively. There were no serious adverse events or adverse reactions reported throughout the study.

Conclusion: After statistical evaluation of the analytical results, the test and reference products were considered bioequivalent. Both products were well tolerated and considered as safe.

Key words: Bioequivalence, bioavailability, dexketoprofen trometamol

INTRODUCTION

Non-steroidal anti-inflammatory/analgesic drugs (NSAIDs) are widely prescribed medications for alleviating pain, fever, and inflammation.¹ A member of NSAIDs, ketoprofen is a chiral 2-arylpropionic acid derivative and a prostaglandin synthesis inhibitor, which is used for its analgesic, anti-inflammatory and antipyretic effects since 1973.² However, the strong prostaglandin synthesis inhibition was attributed to its (S)-(+)-enantiomer in the following years.² Currently, dexketoprofen is considered a member of first-line NSAIDs in the symptomatic

treatment of mild or moderate pain.³ To improve its benefit for treating acute pain, a derivative of more soluble dexketoprofen, has been trometamol, which leads to rapid efficacy.⁴

The rapid onset of action and proven efficacy of dexketoprofen trometamol draws attention of generic pharmaceutical companies whose function is fundamental in drug accessibility. However, a bioequivalence study is required for generic orally administered dexketoprofen trometamol products by European Medicines Agency (EMA).⁵

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Received: 12.04.2022, Accepted: 15.06.2022

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A new generic formulation has been developed by Elixir Pharmaceutical Research and Development Corporation (Ankara, Türkiye) for Tebem İlaç (Ankara, Türkiye) as an alternative to the original brand and to be licensed by the authority, its' bioequivalence needs to be proven. Therefore, this study compares pharmacokinetic properties of a generic formulation to the reference product and to demonstrate bioequivalence of the products with respect to rate and extent of absorption of dexketoprofen trometamol in healthy male volunteers under fasting conditions.

MATERIALS AND METHODS

Study population

All volunteers were healthy adult males (aged 18-55 years) with a body mass index (BMI) within 18.5-30 kg/m². The volunteers who have atopic constitution or asthma and/or known allergy for dexketoprofen trometamol and/or other NSAIDs and/or any excipient of the products were excluded from the study. Volunteers who have any history or presence of clinical relevance of cardiovascular, neurological, musculoskeletal, hematological, hepatic, gastrointestinal, renal, pulmonary, endocrinological, and metabolism disorders were also excluded. History of malabsorption or other conditions that might affect pharmacokinetics of the study drugs, blood donation more than 400 mL within the last two months before the first drug administration, being included in another clinical trial, intake of depot injectable solutions within 6 months and/or intake of enzyme-inducing, organotoxic or long half-life drugs within 4 weeks before the start of the study were among the other exclusion criteria. Regular consuming of beverages or food containing methylxanthines (e.g. coffee, tea, cola, caffeine, chocolate, and sodas) equivalent to or more than 500 mg methylxanthines daily, taking any grapefruit or grapefruit juice during 7 days before drug administration, during the study or during the washout periods, having a history of drug or alcohol abuse and/or having positive alcohol breath test results were counted as exclusion criteria, as well. The inclusion and exclusion criteria were established clearly together with the reasons for withdrawal from the study. The volunteers who were willing to participate in the clinical trial signed a written informed consent form on their own freewill and understood that they could withdraw from the study anytime without specifying any reason.

Study design

A single-center, open-label, randomized, single oral dose, cross-over, two-sequence, two-period study was conducted in 48 healthy, Caucasian adult males under fasting conditions. This study was reviewed and approved by Erciyes University Ethical Committee of Bioequivalence/Bioavailability Studies (2019/03; 16.01.2019) and Turkish Medicines and Medical Devices Agency (20.02.2019) and was held in Türkiye according to the regulations run by the Ministry of Health of the Republic of Türkiye, which comply with Declaration of Helsinki and Good Clinical Principles (GCP).⁶

This study was conducted at FARMAGEN Good Clinical Practice and Research Center (Gaziantep, Türkiye) before the coronavirus disease-2019 era. The clinical study spanned a period of approximately 4 weeks, including pre-study screening (day 14 to 1), wash-out period (7 days), and final examination (2-8 days after the last blood sampling). The standard clinical screening and laboratory examinations in blood and urine were performed and the volunteers were checked for the presence of HBsAg, HCV-Ab, and HIV-Ab in serum. They were requested to provide a urine sample for a drug screening, which includes "amphetamines, cannabinoids, benzodiazepines, cocaine, opioids, and barbiturates" and an alcohol breath test on entry visit and hospitalization days of both periods. The standard clinical screening was included demographic data, brief anamnestic data, physical examination, determination of body temperature, weight and height, standard electrocardiogram (12 lead), measurements of blood pressure, and pulse rate. All laboratory tests were carried out in a certified local laboratory.

A total of 48 volunteers was randomized, and 47 volunteers completed the clinical study. They were admitted to the clinic on the day before dosing day, and after staying 24 h fasted, they received their study drugs. Volunteers were not allowed to drink water from 1 hour before until 1 h after the administration of study products, except while dosing and they remained fasted until 4 h after administration. Immediately after pre-dose sampling, 1 tablet of the test drug or 1 tablet of the reference drug (25 mg dexketoprofen each case), were taken by the volunteers with 240 mL water at ambient temperature. After the washout period (approximately 7 days); in period II, the volunteers were administered the other drug they did not take in the period I. The same procedures were applied in each period.

Investigational medicinal products

The test drug used was dexketoprofen 25 mg film-coated tablet (Tebem İlaç, Türkiye) (batch no: 1809002; expiration date: 09.2020); the reference drug used was Arveles® 25 mg film-coated tablet, UFSA, Türkiye) (batch no: 18180; expiration date: 09.2020).

Blood sampling and study assessment

The samples were drawn by a short intravenous catheter at pre-dose and after ingestion of study products at following points: 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.33, 1.66, 2.00, 2.33, 2.66, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 14.00 h in each clinical study period, and they were collected into polypropylene tubes using K₂EDTA as an anti-coagulating agent.

An evening meal was provided at hospitalization days (total caloric value of approximately 1200 kcal) in each period. On medication days, a standard lunch (total caloric value is approximately 1200 kcal) was provided 4 h after dosing, and a standard dinner (total caloric value is approximately 1200 kcal) was provided 10 h after dosing in each period.

After sampling, the samples were immediately refrigerated at approximately +4°C not more than 30 min. Following the centrifugation (3000 rpm, 4-6°C, 10 min), the separated plasma

from each sample was transferred into two 3 mL transparent, polypropylene tubes, then, transferred to a deep-freeze and stored at -70°C until they were transported to the bioanalytical center.

Determination of plasma concentrations of dexketoprofen

Bioanalytical phase of the study was run using a validated chromatographic method at Novagenix Bioanalytical R&D Center (Ankara, Türkiye). To avoid any bias, the analytical studies were operated as analytically blinded.

Analytical reference standard of dexketoprofen trometamol was supplied from Saurav Chemicals Ltd. (India) and internal standard; (S)-ketoprofen D3 (IS), was supplied from Toronto Research Chemicals, Inc. (Canada). Solvents used including methanol, acetonitrile, and formic acid were supplied from Merck (Germany). Ultrapure (type 1) water was supplied through Millipore MilliQ Water Purification System; K_2EDTA blank human plasma was supplied from Gaziantep University, Farmagen GCP Centre (Türkiye).

A liquid chromatography with tandem mass spectrometry (LC-MS/MS, Waters Acquity) system with a TQ detector was used. An Atlantis HILIC silica $3\ \mu\text{m}$ ($4.6 \times 100\ \text{mm}$) chromatographic column was chosen with a mobile phase consisting of 0.1% formic acid and acetonitrile (35/65, v/v) with a column oven temperature maintained at 40°C . The flow rate was 0.7 mL/min. Electrospray ionization was performed in Multiple reaction monitoring (MRM) mode and positive ion, selective ion monitoring mode was used to detect $m/z\ 255.2 > 209.15$ (dexketoprofen) and $m/z\ 258.2 > 212.3$ [(S)-ketoprofen D3] ions, simultaneously. Total run time for the method was 3.5 min.

Stock standard solutions of dexketoprofen were prepared in methanol at a concentration of 5 mg/mL. Working solutions in the concentration range of 0.4-240 $\mu\text{g}/\text{mL}$ were prepared by diluting stock standard solutions with methanol. The working IS was prepared in methanol at a concentration of 0.2 mg/mL. Stock solutions of dexketoprofen and IS were stored at -20°C . Calibration standards were prepared by spiking the appropriate amounts of standard solutions into blank plasma to obtain final concentration levels between 20-12,000 ng/mL. The quality control samples were prepared similarly at concentrations between 20-9,600 ng/mL. The lower limit of quantification (LLOQ), using 100 μL of human plasma, was 20 ng/mL. Calibration standards and Quality Control (QC) samples were stored at -70°C freezer until the analyses.

For sample preparation, protein precipitation method was preferred to extract dexketoprofen and the samples were prepared according to the bioanalytical center's sample preparation Standard Operating Procedures (SOP).

The method validation was performed with K_2EDTA human plasma according to EMA Guideline on Bioanalytical Method Validation.⁷ The method was validated for selectivity, specificity, carry-over, linearity, precision and accuracy, recovery, dilution integrity, influence of hemolyzed and hyperlipidemic plasma, drug-drug interaction, matrix effect, and stabilities.

The analytical curves were constructed from a blank sample (plasma sample processed without IS), a zero sample (plasma processed with IS) and 8 concentrations of dexketoprofen, including LLOQ, ranging from 20 to 12,000 ng/mL. The concentrations were calculated using peak area ratios and the linearity of the calibration curve was determined using least squares regression analysis employing a weighted ($1/x$) linear ($y: mx + b$) for dexketoprofen. The acceptance criterion for each calculated standard concentration was not more than 15% deviation from the nominal value, except for LLOQ, which was set at 20%. The within-batch precision and accuracy were evaluated by analyzing QC samples at five different concentration levels (LLOQ, QC low, QC medium, QC high, ULLOQ) between 20-9,600 ng/mL with 6 replicates in a batch. The between-batch precision and accuracy were determined by analyzing 3 different batches. The within-batch and between-batch values did not exceed 15% for QC samples, expected for LLOQ, which did not exceed 20%.

The selectivity was studied by checking the chromatograms obtained from 10 different sources of human plasma including one hemolytic and one lipemic plasma. By comparing the chromatograms of those plasma samples spiked with dexketoprofen and IS with the chromatograms of the blank plasma samples, no peak was found at the retention time of dexketoprofen and IS in 10 of the blank plasma samples. The recoveries were estimated by comparing the peak areas of dexketoprofen in 3 replicates of QC samples with those of post-extraction blank matrix extracts at the corresponding concentrations. The matrix effects of dexketoprofen were evaluated by comparing the peak areas of post-extraction blank plasma that were spiked at certain concentrations of QC samples with the areas obtained by the direct injection of the corresponding standard solutions. The stability of dexketoprofen in the plasma samples was determined from three QC levels with 6 replicates each under the following conditions; long-term stability at -70°C for 27 days, short-term stability at room temperature (RT) for 6 h, using processed samples in autosampler vials for 52 h, and after four freeze/thaw cycles (-70°C to RT).

In-house high performance LC-MS/MS detector method was developed and validated to quantify dexketoprofen in plasma.

The plasma samples were maintained at -70°C during the assay. Thawed samples (0.1 mL) at RT were transferred in a polypropylene tube and were prepared for analysis using protein precipitation according to SOPs of bioanalytical center.

Pharmacokinetic and statistical analyses

To demonstrate bioequivalence with a power of 80% and a test/reference parameter ratio between 0.95 and 1.05, 48 volunteers were included in the study to obtain at least 44 completed volunteers.

C_{max} and area under the curve from time 0 to the last measurable concentration ($\text{AUC}_{0-\text{last}}$) were considered the primary target variables; area under the curve from time 0 to the infinite time ($\text{AUC}_{0-\infty}$), time to reach the peak concentration (t_{max}), terminal half-life ($t_{1/2}$), terminal disposition rate constant (λ_z) and mean

residence time (MRT) were declared as the secondary target variables in this bioequivalence study.

C_{max} and t_{max} for dexketoprofen were obtained directly by plasma concentration-time curves. $AUC_{0-t_{last}}$ was calculated using the trapezoidal rule. $AUC_{0-\infty}$ was calculated by summing $AUC_{0-t_{last}}$ and extrapolated area. The latter was determined by dividing the last measured concentration by λ_z , which was estimated by regression of the terminal log-linear plasma concentration time points.

C_{max} and $AUC_{0-t_{last}}$ were tested for statistically significant differences by using Analysis of Variance (ANOVA) test procedure after logarithmic transformation (ln). The effects of ANOVA were treatment, period, and volunteer within the sequence and tested at 5% level of significance.

In the assessment of bioequivalence, the confidence intervals (CI) approach was used. Two one-sided hypothesis at the 5% level of significance was tested by constructing the 90% CIs for the geometric mean ratios of test/reference products. Two formulations were considered as bioequivalent, if the 90% CIs were within 80.00-125.00% for C_{max} and $AUC_{0-t_{last}}$. The difference in t_{max} was evaluated non-parametrically.

All statistical analyzes were performed using Phoenix WinNonlin (version 8.1, Certara L.P.).

Also, ANOVA and determination of 90% CIs were applied to non-logarithmic transformed data of t_{max} , $t_{1/2}$, λ_z , and MRT and to ln transformed data of $AUC_{0-\infty}$.

RESULTS

Sixty-nine volunteers were screened, while 48 volunteers were randomized and included in the study. The volunteers were divided into two groups according to the randomization table. There was one drop-out from the study, who did not want to continue the trial by his freewill before dosing in period II. As a result, 47 volunteers completed the clinical phase of the study. All the volunteers were Caucasian. The mean \pm standard deviation (SD) age of volunteers was 26.72 ± 7.85 years and the mean \pm SD BMI was 24.86 ± 2.74 . The demographic data for volunteers are presented in Table 1. There was no protocol deviation through the clinical period. The actual time of sampling was used in the estimation of the pharmacokinetic parameters. In Period II, there was no pre-dose drug concentrations observed, which indicated that the washout period of 7 days was sufficient.

The pharmacokinetic parameters for test and reference products are summarized in Table 2 and the geometric least

Table 1. Demographic data of the volunteers

n: 47	Age	Weight (kg)	Height (cm)	BMI
Mean	26.72	78.49	177.72	24.86
SD	7.85	9.12	5.97	2.74
Minimum	19	60	170	18.83
Maximum	53	95	195	29.75

SD: Standard deviation, BMI: Body mass index

square means, ratios, and 90% CIs are summarized in Table 3. Average plasma concentration-time curves and average ln plasma concentration-time curves of test and reference products for a single dose of dexketoprofen are displayed in Figures 1 and 2, respectively.

For the test and reference products, the mean \pm SD of C_{max} was found 2543.82 ± 655.42 ng/mL and 2539.11 ± 662.57 ng/mL, and the mean \pm SD of $AUC_{0-t_{last}}$ was found 3483.49 ± 574.42 h.ng/mL and 3560.75 ± 661.83 h.ng/mL, respectively (Table 2).

The primary target variables data demonstrate bioequivalence of test and reference products regarding 90% CI for C_{max} of 92.45-108.53 and for $AUC_{0-t_{last}}$ of 95.57-100.87, which are within acceptance limits (80.00-125.00%).⁴ The geometric mean ratios were found as 100.16% and 98.18% for C_{max} and $AUC_{0-t_{last}}$ respectively (Table 3).

For the secondary endpoint data, the median of t_{max} for both the test and reference products were found 0.5 h and ranged from 0.33 h to 1.33 h for the test product, and 0.33-1.66 h for the reference product. Besides, the mean \pm SD of $t_{1/2}$ for the test and reference products was found 1.88 ± 1.09 h (ranged from 1.16 h to 7.08 h) and 1.94 ± 1.24 h (ranged from 1.69 h to 9.09 h), respectively. The mean \pm SD of λ_z for the test and reference product was 0.42 ± 0.11 1/h (ranged from 0.1 1/h to 0.6 1/h) and 0.42 ± 0.12 1/h (ranged from 0.08 1/h to 0.63 1/h), respectively (Table 2).

Safety and tolerability

There were 3 possible and 4 unlikely associated drug-related adverse events occurred in all two periods. Five of 7 adverse events were fully recovered. One volunteer received concomitant medication (paracetamol) due to a headache complaint. The severity and seriousness of adverse events and

Table 2. The arithmetic mean \pm SD of pharmacokinetic parameters of single oral dose of 25 mg dexketoprofen in the test drug (dexketoprofen 25 mg film-coated tablet, Tebem İlaç, Türkiye); the reference drug used was (Arvels® 25 mg film-coated tablet, UFSA, Türkiye) in healthy adult male volunteers under fasting conditions (arithmetic mean \pm SD, n: 47)

Parameters (units)	Test (T)	Reference (R)
C_{max} (ng/mL)	2543.82 ± 655.42	2539.11 ± 662.57
$AUC_{0-t_{last}}$ (ng.h/mL)	3483.49 ± 574.42	3560.75 ± 661.83
$AUC_{0-\infty}$ (ng.h/mL)	3562.44 ± 587.99	3640.81 ± 694.17
t_{max} (h)*	0.61 ± 0.28 (0.33-1.33)	0.66 ± 0.32 (0.33-1.66)
$t_{1/2}$ (h)	1.88 ± 1.09	1.94 ± 1.24
λ_z (1/h)	0.42 ± 0.11	0.42 ± 0.12
MRT (h)	2.03 ± 0.50	2.05 ± 0.63

* t_{max} values are presented as median with range (minimum - maximum) in parentheses. SD: Standard deviation, $AUC_{0-t_{last}}$: Area under the curve from time 0 to the last measurable concentration, $AUC_{0-\infty}$: Area under the curve from time 0 to the infinite time, t_{max} : Time to reach the peak concentration, $t_{1/2}$: Terminal half-life, λ_z : Terminal disposition rate constant, MRT: Mean residence time

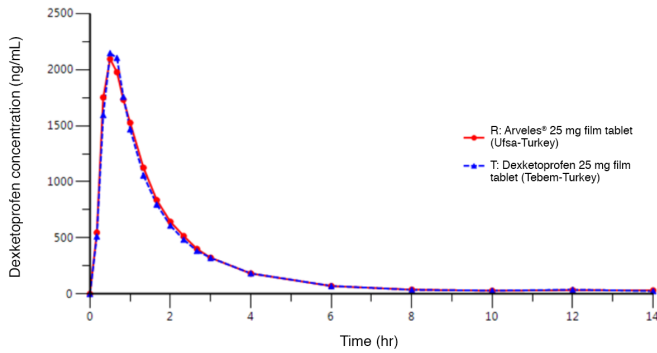


Figure 1. Mean plasma concentration-time curves of dexketoprofen after a single dose of the test drug (dexketoprofen 25 mg film tablet, Tebem İlaç, Türkiye) and the reference drug (Arveles® 25 mg film-coated tablet, UFSA, Türkiye) of oral dexketoprofen in healthy adult male volunteers under fasting conditions (n: 47)

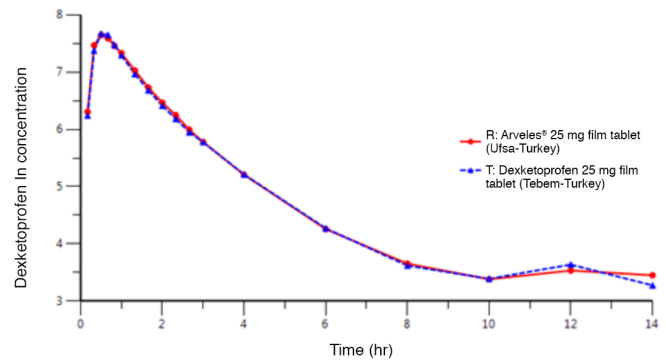


Figure 2. Average ln plasma concentration curves of dexketoprofen after a single dose of the test drug (dexketoprofen 25 mg film-coated tablet, Tebem İlaç, Türkiye) and the reference drug (Arveles® 25 mg film-coated tablet, UFSA, Türkiye) of oral dexketoprofen in healthy adult male volunteers under fasting conditions (n: 47)

Table 3. Geometric least square means, ratio, and 90% confidence intervals of the test drug (dexketoprofen 25 mg film-coated tablet, Tebem İlaç, Türkiye) and the reference drug (Arveles® 25 mg film-coated tablet, UFSA, Türkiye) in healthy adult male volunteers under fasting conditions

Parameter	Difference	DiffSE	TESTLSM	REFLSM	Ratio%	90% CI	ISCV%
$\ln(C_{\max})$	0.0016	0.0477	7.8022	7.8005	1.0016	0.9245 – 1.0853	23.45
$\ln(AUC_{0-t_{\text{last}}})$	-0.0183	0.0161	8.1419	8.1602	0.9818	0.9557 – 1.0087	7.81
$\ln(AUC_{0-\infty})$	-0.0174	0.0161	8.1643	8.1817	0.9827	0.9566 – 1.0096	7.79
t_{\max} (h)	-0.0512	0.0474	0.6095	0.6607	0.9225	0.8019 – 1.0431	
$t_{1/2}$ (h)	-0.0639	0.0915	1.8753	1.9391	0.9671	0.8878 – 1.0463	
λ_z (1/h)	0.0033	0.0141	0.4202	0.4169	1.0078	0.9512 – 1.0645	

$AUC_{0-t_{\text{last}}}$: Area under the curve from time 0 to the last measurable concentration, $AUC_{0-\infty}$: Area under the curve from time 0 to the infinite time, t_{\max} : Time to reach the peak concentration, $t_{1/2}$: Terminal half-life, λ_z : Terminal disposition rate constant, CI: Confidence interval, DiffSE: Standard error of the difference in least square mean, TESTLSM: Test least square mean, REFLSM: Reference least square mean, ISCV: Intra-subject coefficient of variation

the overall tolerability of the products were considered as mild. There were no serious adverse events or adverse reactions reported throughout the study.

DISCUSSION

Dexketoprofen trometamol is a widely prescribed molecule in symptomatic treatment of mild or moderate pain and its place in the NSAID market, especially in the pharmaceutical industry specialized on generic drugs is remarkable. A novel formulation of dexketoprofen trometamol, which is aimed to be licensed and presented to the pharmaceutical market, was developed and according to the current regulations, where the pharmacokinetic properties were assessed in a bioequivalence study.

ANOVA results exhibited that treatment, sequence, period, and volunteer within sequence had no statistically significant effects on C_{\max} and $AUC_{0-t_{\text{last}}}$ (except volunteer within sequence effect for only $AUC_{0-t_{\text{last}}}$). Since the sequence or carry-over effect was not significant, ANOVA was valid.

Besides, ISCVs were found as 23.45% and 7.81% and the geometric mean ratios were found as 100.16% and 98.18% for C_{\max} and $AUC_{0-t_{\text{last}}}$, respectively.

Study limitations

To acquire a standardized environment and reach an optimum sample size, only male populations were selected in this study. Therefore, the pharmacokinetic parameters of dexketoprofen be different among females.

CONCLUSION

Since the 90% CIs for the test/reference geometric mean ratios for C_{\max} and $AUC_{0-t_{\text{last}}}$ of dexketoprofen are contained within the acceptance limits, 80.00-125.00%, according to the applied bioequivalence study, it is concluded that test and reference dexketoprofen trometamol products are bioequivalent under fasting conditions. Therefore, newly formulated generic dexketoprofen 25 mg tablets can be licensed under the requirements of regulatory authorities. Moreover, both study drugs were well-tolerated and considered safe.

ACKNOWLEDGMENTS

This study was sponsored by Tebem İlaç (Ankara, Türkiye). The test drug product was developed by Elixir Pharmaceutical Research and Development Corporation (Ankara, Türkiye) and the biobatch of the test drug product was manufactured by

Gen İlaç ve Sağlık Ürünleri San. ve Tic. A.Ş. (Ankara, Türkiye) under current Good Manufacturing Practices (GMP). The bioequivalence study was conducted by FARMAGEN Good Clinical Practice and Research Center (Gaziantep, Türkiye) and the bioequivalence analysis was carried out by Novagenix Bioanalytical Drugs R&D Centre (Ankara, Türkiye).

Ethics

Ethics Committee Approval: This study was reviewed and approved by the Erciyes University Ethical Committee of Bioequivalence/Bioavailability Studies (2019/03; 16.01.2019) and Turkish Medicines and Medical Devices Agency (20.02.2019).

Informed Consent: Written informed consent obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.S., S.P.A., Concept: F.Y., O.S., S.P.A., Design: F.Y., O.S., S.P.A., A.A., H.B., Data Collection or Processing: F.Y., O.S., Analysis or Interpretation: F.Y., O.S., Literature Search: F.Y., A.A., H.B., Writing: F.Y., S.P.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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