

FASTING AND FED BIOEQUIVALENCE STUDIES OF ETODOLAC SUSTAINED RELEASE TABLETS MANUFACTURED IN TURKEY IN HEALTHY VOLUNTEERS

Abdullah Uslu¹, İlksen Dikmen¹, Seda Ünsalan², Berrak Kılınç³, Onursal Sağlam³, Aydın Erenmemişoğlu⁴, İclal Çakıcı², Ömer Ocak²

¹Nobel İlaç Ar-Ge Merkezi, Düzce,

²Nobel İlaç, İstanbul,

³NOVAGENIX Biyoanalitik Ar-Ge Merkezi, Ankara,

⁴Erciyes Üniversitesi, Hakan Çetinsaya İKU Merkezi, Kayseri

ABSTRACT

Objective: The current study was designed to compare the pharmacokinetic properties and tolerability of the newly developed sustained release (SR) tablet of etodolac 600 mg (NOBEL ILAC, Turkey), with those of the conventional tablet of the marketed innovator formulation, Lodine SR tablet, 600 mg from Almirall Ltd, England, administered into healthy male subjects in fasting and fed conditions.

Material and Method: Both fasting study and fed study were a single centre, open-label, randomised, single oral dose, cross-over, two sequence, two-period study. 36 subjects were randomly assigned into 2 groups according to a computer-generated randomization scheme. The subjects in group 1 received the reference formulation in Period 1 and the test formulation in Period 2, and those in group 2 vice

versa, with a 7 day washout period between Periods 1 and 2. Totally 21 blood sample points were selected including predose. The determination of etodolac was performed using a validated high performance liquid chromatography occupied with UV (HPLC-UV) in lithium heparinised human plasma.

Results: Pharmacokinetic findings showed that the newly developed SR tablet of NOBEL ILAC was bioequivalent to the marketed innovator formulation in healthy population under fasting and fed conditions.

Conclusions: Results indicated that the new SR formulation of NOBEL ILAC can be used interchangeably with the formulation of the innovator.

Keywords: Etodolac, bioequivalence, sustained release (SR) tablet, pain. *Nobel Med* 2016; 12(2): 53-59

TÜRKİYE'DE ÜRETİLEN ETODOLAK İÇEREN UZATILMIŞ SALIMLI TABLETLERİN SAĞLIKLI GÖNÜLLÜLERDE AÇLIK VE TOKLUK KOŞULLARINDA YAPILAN BİYOEŞDEĞERLİK ÇALIŞMALARI

ÖZET

Amaç: Bu çalışmanın amacı, NOBEL İLAÇ tarafından yeni geliştirilen uzatılmış salımlı (SR) formülasyonun, (Etodolac SR Tablets, 600 mg) sağlıklı erkek gönüllülerdeki farmakokinetiği ve tolere edilebilirliğinin inovatörün pazarda mevcut SR dozaj formundaki tableti olan Lodine SR Tablets 600 mg (Almirall Limited, England) ile karşılaştırılmasıdır.

Materyal ve Metot: Hem açlık hem de tokluk çalışması, tek merkezli, açık etiketli, randomize tek doz, çapraz geçişli iki sıralı iki periyotlu bir çalışma idi. Otuzaltı gönüllü bilgisayar kaynaklı randomizasyon tablosuna göre iki gruba ayrılmıştır. 1. gruptaki gönüllüler 1.

periyotta referans ürünü, 2. periyotta test ürünü almışlar, ve 1 ve 2 periyot arasındaki 7 günlük arınma süresi sonrası, 2. gruptakilere tam tersi olacak şekilde uygulama yapılmıştır. Dozlama öncesi dahil, 21 kan alım noktası seçilmiştir. Lityum heparinli insan plazmasında etodolakin tayini, valide edilmiş bir HPLC -UV metodu ile yapılmıştır.

Bulgular: Farmakokinetik bulgular, Nobel ilaç tarafından geliştirilen yeni SR tablet formülasyonun sağlıklı gönüllülerde açlık ve tokluk koşullarında, pazarda bulunan inovatör formülasyona biyoeşdeğer olduğunu göstermiştir.

Sonuç: Bulgular, NOBEL İLAÇ tarafından geliştirilen yeni SR formülasyonunun, tedavide inovatörün formülasyonu yerine kullanılabileceğini göstermektedir.

Anahtar kelimeler: Etodolac, biyoeşdeğerlik, uzatılmış salımlı (SR) tablet, ağrı. *Nobel Med 2016; 12(2): 53-59*

INTRODUCTION

Etodolac is an anti-inflammatory agent that potently and selectively inhibits COX-2 while preserving COX-1 activity, and is widely used to alleviate symptoms associated with osteoarthritis.¹⁻⁴

Etodolac exhibits linear pharmacokinetics, good oral bioavailability, greater than 99% protein binding, a low oral clearance (almost exclusively non-renal), a relatively small volume of distribution and a half-life that averages 7.3±4.0 h. The pharmacodynamics of the drug are well characterized in terms of pain intensity differences (PID) yielding an EC₅₀ of 13 micrograms/ml. The extensive kinetic/dynamic characterization of etodolac, together with its short half-life, makes the drug an ideal candidate for a sustained-release (SR), once-a-day formulation. Etodolac SR formulations exhibit the same pharmacokinetic characteristics as the conventional-release (CR) formulation, except for a longer time to peak concentration and a lower peak concentration. Fluctuation ratios upon multiple dosing are comparable for equal total daily doses of etodolac SR and twice-daily doses of the CR formulation. Administration with food (high-fat meal) did not affect areas under the curve for either the CR or the SR product. Simulation analyses for etodolac SR suggest that PID responses are maintained over 24 h.⁵⁻⁷

The current study was designed to compare the pharmacokinetic properties and tolerability of the newly

developed etodolac SR tablet 600 mg, with those of reference drug, Lodine SR tablet 600 mg administered concomitantly in healthy male subjects in fasting or fed conditions.

MATERIAL AND METHOD

Subjects

Eligible subjects were healthy male volunteers between the ages of 18 and 55 years having the body mass index ranged between 18.5-30 kg/m² and with no congenital abnormality or chronic disease. Key exclusion criteria included: history of hypersensitivity to etodolac; history of cardiovascular, pulmonary, renal, endogenous, gastrointestinal, hematologic, neurologic, or hemorrhagic disease; clinically significant findings on routine laboratory tests (serology, hematology, serum chemistry, and urinalysis); hypotension (systolic blood pressure (BP)≤100 mm Hg or diastolic BP≤65 mm Hg) or hypertension (systolic BP≥150 mm Hg or diastolic BP≥100 mm Hg); use of prescription drugs or herbal medications within 2 weeks or use of nonprescription drugs within 1 week before the study that had the potential to interact with etodolac; and use of drugs that induce or inhibit drug-metabolizing enzymes within 1 month before the study that had the potential to interact with study medication.

The Clinical Study Protocol (dated on 13.09.2011), and Informed Consent Form (dated on 13.09.2011)

and Case Report Form (dated on 13.09.2011) of the fasting study were approved by appointed local ethics committee in Kayseri on 19.09.2011 (Decree No:2011/13) and by Turkish Medicines & Medical Devices Agency, Republic of Turkey- Ministry of Health on 07.10.2011.

The Clinical Study Protocol (dated on 22.02.2012), and Informed Consent Form (dated on 22.02.2012) and Case Report Form (dated on 22.02.2012) of the fed study were approved by appointed local ethics committee in Kayseri on 12.03.2012 (Decree No: 2012/46) and by Turkish Medicines & Medical Devices Agency, Republic of Turkey- Ministry of Health on 21.03.2012.

These studies were performed in accordance with the Declaration of Helsinki and were also in accordance with the relevant laws and regulations of Turkey where the trials were performed, as well as any applicable international guidelines on GCP and GLP.⁸⁻¹² All subjects gave written informed consent before study enrollment.

Drug Products

The following formulations were used:

Test Drug; Etodolac SR Tablets, 600 mg

Manufacturer: Nobelfarma Ilac Sanayii ve Ticaret A.S, Turkey
Marketing authorisation holder: Nobel Ilac San. ve Tic. A.S, Turkey

Reference Drug; Lodine SR Tablets 600 mg

Manufacturer: Industrias Farmaceuticas Almirall Prodesfarma S.L-Spain

Marketing Authorisation Holder: Laboratorios Almirall SA, Spain Marketing site: Almirall Limited-UK

Design of Fasting Study

This study was randomized, open-label, single-dose, 2-way crossover. Subjects (n=36) were randomly assigned into 2 groups according to a computer-generated randomization scheme (Randomisation Generator by Jonathan Goddard) and received the test and the reference formulations alternatively.³⁶ healthy male subjects (intention to treat population) received one single oral dose of 600 mg etodolac SR or one tablet of Lodine SR 600 mg tablet at once after a overnight fast in each period according to a sequence determined by randomisation.

The subjects in group 1 received the reference formulation in Period 1 and the test formulation in Period 2, and those in group 2 vice versa, with a 7-day washout period between Period 1 and Period 2. Studied drugs were administered with 240 mL water on the Days 1.

The subjects were fasted overnight (at least 10 hours) and drug administration took place in the morning between 07:00 and 09:00 and the exact time was recorded on CRFs. Subjects were not allowed to drink water from 1 h before until 1 h after administration, except while drug administration. The subjects remained fasting until 4 hours after administration. Subjects were dosed in sitting position; during the next 4 hours they remained sitting or standing but not supine position. Standard meals containing 1200 kcal were provided for lunch and dinner to both groups at 4 and 10 hours after dosing, respectively.

Design of Fed Study

This was a crossover study; each subject received two formulations according to a crossover design. The elimination half-life of etodolac was given as 8.4 hours in literatures. The last sampling time evaluated as 5 times of $t_{1/2}$ which was found 42 hours. The period of 72 hours sampling in this study was judged to be sufficient to characterise the concentration-time curve. The wash-out period was evaluated as 10 times of $t_{1/2}$ which was found as 84 hours (3.5 days). Therefore, the two dosing periods were separated by a wash-out period of at least 7 days to minimize the carry-over effect. This design was based on the fact that the cross-over increases the statistical test power. Each subject was considered as his own control.

The tablets (one tablet containing 600 mg etodolac) were given each 36 subjects included in the study 2 times (once at each study period) by oral route with 240 mL water at room temperature. The subjects were overnight fasted at least 12 hours, until the standard breakfast (2 eggs fried in 10 g butter, 100 g of sausage, 2 slices of toast with 10 g butter, 113 g of hash brown potatoes with 10 g butter, 240 mL of whole milk) was given to the subjects 30 min before drug administration. The breakfast has been completed at least 5 minutes before the application of tablets.

Lunch and dinner times were 4 hours and 10 hours after the medication for all periods, respectively. All periods' meal menus were the same to minimize the food effect.

Blood Sampling

Venous blood samples were collected into polypropylene tubes containing lithium heparinate as anti-coagulating agent by an indwelling catheter inserted into the forearm;

at 0 (predose) and 1.00, 2.00, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.33, 6.66, 7.00, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 hours after dosing for the test and the reference drugs for the fasting study and;

n*=36	Age	Weight (kg)	Height (cm)
Mean	25.47	70.64	175.50
SD	4.99	10.26	6.51
Minimum	18	50	160
Maximum	38	99	185
Subject 03**	18	68	170
Subject 28**	20	81	183

*: All subjects were Caucasian male, **: dropped-out subject, SD: standart deviation

n*=36	Age	Weight (kg)	Height (cm)
Mean	26.08	72.50	174.83
SD	6.48	10.74	5.41
Minimum	18	56	160
Maximum	41	93	185

*: All subjects were Caucasian male, SD: standart deviation

at 0 (predose) and 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 6.50, 7.00, 7.33, 7.66, 8.00, 8.50, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after dosing for the test and the reference drugs for the fed study.

Tubes containing blood samples were placed in tube holder in ice-cold water. The blood samples (8 mL) were collected into tubes containing lithium heparinate as anti-coagulating agent. The total amount of blood taken from each volunteer was approximately 336 mL for fasting study and 364 mL for fed study. This amount did not include blood for screening and post-study tests for both studies (approximately 60 mL). After sampling the blood samples for pharmacokinetic analysis, the tubes were immediately refrigerated at approximately +4°C and were remained there for not more than 30 minutes. After centrifugation (3.000 rpm, 4-6°C, 10 min), the separated plasma from each sample was transferred into two 3 mL transparent, polypropylene tubes per sample (at least 1.5 mL per tube), were transferred to a deep-freezer and were stored at -70°C. At the end of the study one aliquots were shipped on dry ice (solid CO₂) according to the sample transport SOP of DEKAM-İKU by courier for the determination of plasma drug concentrations to the analytical laboratory.

As precautionary measure, the other aliquots were at first retained at the clinical unit in case that additional measurement, for example due to transport damage of the first shipment, and were sent in the day after. The procedure was same for fed study.

Bioanalysis

A procedure for the quantitative determination of etodolac in lithium heparinate human plasma using high performance liquid chromatography occupied with UV was developed and validated at Novagenix Bioanalytical Drug R&D Centre, (Ankara, Turkey). The analysis samples were prepared with liquid-liquid extraction by using 0.25 mL of human plasma. The method was validated in a range of 0.2-100 µg/mL for etodolac. The calibration range and concentration levels of quality control samples were changed; therefore the partial validation report was prepared in addition to the full validation report. This method was valid over the range of 0.2-50 µg/mL for etodolac.

Results were found that accuracy and precision of this method were within the acceptance range according to FDA and EMA Guidelines and other cited references.¹³⁻¹⁷

Tolerability Assessments

The initial examination was carried out not more than 14 days before the beginning of the trial (first study Period). The standard clinical screening included demographic data, brief anamnestic data (medical history with information about relevant previous diseases of all body systems), physical examination, determination of body temperature (axillar), weight and height, standard ECG (12 lead), measurements of BP and pulse rate (PR) after 5 minutes supine rest.

All of the clinical laboratory tests mentioned below were performed at a contracted and certified laboratory (Central Laboratory of Erciyes University, School of Medicine-Kayseri).

The standard laboratory screening included serum levels of "CBC, glucose, urea, uric acid, creatinine, total bilirubin, sodium, potassium, calcium, chloride, SGOT (AST), SGPT (ALT), GGT, alkaline phosphatase, total protein and urinalysis". The blood specimen for the safety laboratory was taken under fasting and fed conditions. Total blood sampling for both laboratory examinations (entry and final) was 60 mL for both studies. The volunteers were checked for presence of HBsAg, HCV-Ab and HIV-Ab in serum.

The following parameters were determined in urine (30 mL): pH, protein, glucose (semiquantitatively by means of strip test), ketones, blood, leukocytes, bilirubin, nitrites. If the strip test for any urine parameter was positive, a microscopic examination of the sediment was done.

At entry visit and hospitalization days of Period I and Period II, the volunteers were requested to provide a urine sample for a drug screen including "amphetamines,

cannabinoids, benzodiazepines, cocaine, opioids and barbiturates". A list of the normal ranges and units of measurement of the laboratory parameters to be determined during the study and the certificate of the laboratory were provided by the investigator before the start of the study. The reference ranges and the results of the individual laboratory examination were documented in CRFs. The investigator was provided with a print-out or authorized copy of the original laboratory values. The test and reference products were administered under fasting and fed conditions each in a randomised manner in two-period with at least 7 days wash-out period. Volunteers were treated under hospitalization conditions on Day 1 of either Period and were hospitalised at the Clinical Facility (Hakan Çetinsaya-İKU) from the evening of Day 0 (hospitalization day) normally until the 24:00 ($t_{16,00}$) in Day 1 (medication day) to ensure volunteers' safety as well as standardised trial conditions during profiling days (e.g. in view of food and fluid intake, diet, fasting conditions, drug administration, clinical and other procedures). Adverse events (AEs) were monitored in the course of the study. Subsequently, volunteers came to the clinic 3 more times ($t_{24,00}$, $t_{36,00}$ and $t_{48,00}$) during fasting study and 4 more times ($t_{24,00}$, $t_{36,00}$, $t_{48,00}$ and $t_{72,00}$) during fed study per period for blood samples. The medical care of the volunteers was guaranteed by the presence or stand-by of the investigator or one of the co-investigators throughout the clinical phase of this trial.

During both fasting and fed studies, the volunteers came to the clinic at approximately 18:00 on the day before the treatment (Day 0) of each Period and remained there for 30 hours. A measurement of body temperature (axillar) was performed in the evening before each in-house Period. The investigator checked on each volunteer's well-being prior to their discharge from the clinic. All volunteers were subjected to a post-study examination and laboratory tests on the day of last sampling in second Period or not more than 7 days thereafter.

Statistical Analysis

Assessment of comparative bioavailability was based on 90% Confidence Intervals (CIs) for geometric mean ratios (test to reference drug) for the primary pharmacokinetic parameters (C_{max} and AUC_{0-48} for fasting study and C_{max} and AUC_{0-72} for fed study) of etodolac. As defined by the Turkish Medicines and Medical Devices Agency, Republic of Turkey Ministry of Health, and international guidelines (ICH, EMA and FDA Guidelines); studied drugs were assumed to be bioequivalent, if 90% CIs for the treatment ratios of the primary parameters were within the range of 0.80 to 1.25.

Table 3. Pharmacokinetic results of the fasting study

Parameters (Units)	Arithmetic Mean±SE (n=36)	
	Test (T)	Reference (R)
C_{max} (µg/mL)	10.980±0.519	11.008±0.520
$AUC_{0-t_{last}}$ (µg.hr/mL)	178.487±9.546	191.408±9.400
$AUC_{0-\infty}$ (µg.hr/mL)	188.216±10.780	199.474±10.635
t_{max} (hr)	7.343±0.599	7.528±0.674
$t_{1/2}$ (hr)	8.384±0.378	8.335±0.390
λ_z (1/hr)	0.087±0.001	0.088±0.001
MRT (hr)	16.561±0.613	16.974±0.565

C_{max}: Maximum concentration; **AUC_{0-t_{last}}**: area under the plasma concentration-time curve from zero to the last measurable concentration; **AUC_{0-∞}**: area under the plasma concentration-time curve from zero up to the infinity; **t_{max}**: time to reach the maximal concentration; **t_{1/2}**: terminal half-life; **λ_z**: elimination rate constant; **MRT**: mean residence time; **Test Drug**: etodolac SR tablets, 600 mg; **Reference Drug**: lodine SR tablets 600 mg

Table 4. Pharmacokinetic Results of the fed study

Parameters (Units)	Arithmetic Mean±SE (n=36)	
	Test (T)	Reference (R)
C_{max} (µg/mL)	29.332±1.348	24.980±1.018
$AUC_{0-t_{last}}$ (µg.hr/mL)	250.740±13.764	249.842±15.007
$AUC_{0-\infty}$ (µg.hr/mL)	257.427±14.626	258.109±16.319
t_{max} (hr)	4.917±0.188	5.023±0.196
$t_{1/2}$ (hr)	8.833±0.499	9.092±0.505
λ_z (1/hr)	0.084±0.001	0.082±0.001
MRT (hr)	13.339±0.697	13.689±0.711

C_{max}: Maximum concentration; **AUC_{0-t_{last}}**: area under the plasma concentration-time curve from zero to the last measurable concentration; **AUC_{0-∞}**: area under the plasma concentration-time curve from zero up to the infinity; **t_{max}**: time to reach the maximal concentration; **t_{1/2}**: terminal half-life; **λ_z**: elimination rate constant; **MRT**: mean residence time; **Test Drug**: Etodolac SR Tablets, 600 mg; **Reference Drug**: Lodine SR Tablets 600 mg

Demographic data of volunteers was shown in Table 1 for the fasting study and Table 2 for the fed study.

RESULTS

This current study was open-labelled study. Only the CRO was blinded itself to avoid any bias. All the analytical analyses were done without the knowledge of the Test and the Reference products. All CRO staff knew the products only as Product A or Product B during analysis. After the laboratory analysis was completed the code was broken by a commission consisting of clinical director, laboratory analytical director and Information technology director and with their assistants.

FASTING STUDY

Study Subjects

Forty-three subjects were screened and 36 subjects were randomised and included into the study. The subjects were divided into two groups according to the randomisation table.

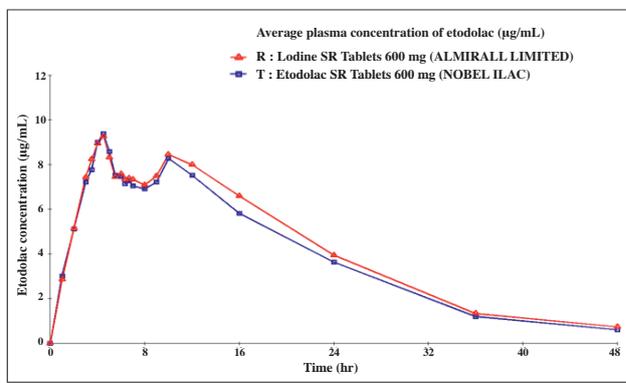


Figure 1. Average plasma concentration of etodolac for fasting study.

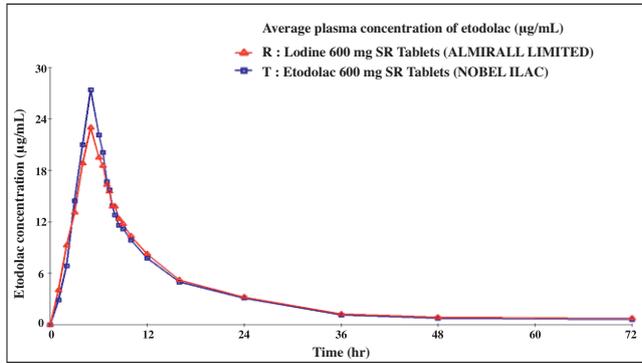


Figure 2. Average plasma concentration of etodolac for fed study.

Table 5. Statistical results of the fasting study							
Parameter	Difference	DiffSE	TESTLSM	REFLSM	Ratio [%Ref]	90% CI	Intrasubject CV
$\ln(C_{max})$	0.0011	0.0388	2.3619	2.3608	1.0011	0.9375-1.0690	16.6
$\ln(AUC_{0-12hr})$	-0.0766	0.0414	5.1350	5.2116	0.9262	0.8636-0.9934	17.7
$\ln(AUC_{0-\infty})$	-0.0609	0.0395	5.1822	5.2431	0.9409	0.8800-1.0060	16.7
t_{max} (hr)	-0.1853	0.9349	7.3425	7.5278	0.9754	0.7653-1.1854	
$t_{1/2}$ (hr)	0.0520	0.2641	8.3843	8.3322	1.0062	0.9526-1.0599	
λ_z (1/hr)	-0.0011	0.0024	0.0873	0.0884	0.9877	0.9423-1.0330	
MRT (hr)	-0.3796	0.5315	16.5613	16.9409	0.9776	0.9245-1.0307	

C_{max} : Maximum concentration, AUC_{0-12hr} : area under the plasma concentration-time curve from zero to the last measurable concentration, $AUC_{0-\infty}$: area under the plasma concentration-time curve from zero up to the infinity, t_{max} : time to reach the maximal concentration, $t_{1/2}$: terminal half-life, λ_z : elimination rate constant, MRT: mean residence time, CI: confidence interval.

There were 2 drop-outs:

In Period I: Subject 03 did not want to continue to the trial and dropped out.

In Period II: Subject 28 was completed first Period of trial. But during the second Period after dosing volunteer vomited and dropped out.

They were replaced with Subject 03R, and 28R, respectively. Test product administered to 37 subjects; reference product administered to 38 subjects (including dropout subjects). Thirty-six subjects completed the clinical phase of the study as planned.

Pharmacokinetics and Statistics

The mean plasma concentration-time profiles and the pharmacokinetic and statistical parameters after the test and the reference drugs were depicted in the Figure

1, Table 3 and Table 5. The 90% CIs for the geometric mean ratio of the primary parameters were all within the comparative bioavailability range of 0.8 to 1.25.

The mean C_{max} were 10.980 $\mu\text{g/mL}$ (for test product) and 11.008 $\mu\text{g/mL}$ (for reference product). The mean AUC_{0-12hr} were 178.487 $\mu\text{g}\cdot\text{hr/mL}$ (for test product) and 191.408 $\mu\text{g}\cdot\text{hr/mL}$ (for reference product). The mean times to reach the maximal concentration were 7.343 hours (for test product) and 7.528 hours (for reference product) after drug administrations. The mean terminal half-lives of etodolac were 8.384 hours (for test product) and 8.335 hours (for reference product) after drug administrations. Considering that 90% confidence interval values for the test/reference mean ratios of the C_{max} and AUC_{0-12hr} were contained within the acceptance limits preset in the Clinical Study Protocol, 0.80-1.25; according to the applied bioequivalence study, it was concluded that test and reference etodolac products were bioequivalent.

FED STUDY

Study Subjects

Fifty subjects were screened. Thirty-six subjects were randomised and included into the study. The subjects were divided into two groups according to the randomisation table.

There was no drop-outs. After 7 days washout period; in Period II, the subjects were administered by the other drug that they were not administered in the Period I. Thirty-six subjects completed the clinical phase of the study as planned.

Pharmacokinetics and Statistics

The mean plasma concentration-time profiles and the pharmacokinetic and statistical parameters of etodolac after the test and the reference drugs were depicted in the Figure 2, Table 4 and Table 6 for the fed study. The 90% CIs for the geometric mean ratio of the primary parameters were all within the comparative bioavailability range of 0.8 to 1.25.

In each period, one tablet containing 600 mg etodolac was given as a single oral dose to obtain the measurable plasma concentrations of etodolac. The mean times to reach the maximal concentration were 4.917 hours (for test product) and 5.023 hours (for reference product). The mean terminal half-lives of etodolac were 8.833 hours (for test product) and 9.092 hours (for reference product) after drug administrations (For details see Table 4). All of these parameters given above were in agreement with values previously reported in the literatures. The mean C_{max} were 29.332 $\mu\text{g/mL}$ (for test product) and 24.980 $\mu\text{g/mL}$ (for reference

product). The mean $AUC_{0-t_{last}}$ were 250.740 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (for test product) and 249.842 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (for reference product). Considering that 90% confidence interval values for the test/reference mean ratios of the C_{max} and $AUC_{0-t_{last}}$ were contained within the acceptance limits preset in the Clinical Study Protocol, 0.80-1.25; according to the applied bioequivalence study, it was concluded that test and reference etodolac products were bioequivalent.

TOLERABILITY

During both fasting and fed study, the test and the reference drugs were well tolerated in all subjects. All AEs were mild or moderate and no serious AEs were observed. Most of the subjects who reported to have an AE recovered spontaneously within a few hours or a few days of drug administration. No clinically significant change was found in results of physical examinations, vital signs, laboratory tests, or ECG results when judged by clinicians (performed unmasked because it was an open-label study).

DISCUSSION

Present studies aimed to investigate if SR formulation of NOBEL ILAC was bioequivalent to those of innovator product and results showed that the newly developed SR tablet of NOBEL ILAC was bioequivalent to the reference (Lodine SR 600 mg) product in this healthy population both in fasting and fed conditions, based on the regulatory criteria for bioequivalence. AEs were mild to moderate, and no serious AEs were reported. Among the subjects who withdrew from the study, none

Parameter	Difference	DiffSE	TESTLSM	REFLSM	Ratio [%Ref]	90% CI	Intrasubject CV
$\ln(C_{max})$	0.1526	0.0268	3.3374	3.1848	1.1649	1.1133-1.2189	11.4
$\ln(AUC_{0-t_{last}})$	0.0040	0.0143	5.4725	5.4684	1.0040	0.9800-1.0286	6.1
$\ln(AUC_{0-\infty})$	-0.0005	0.0139	5.4973	5.4978	0.9995	0.9763-1.0233	5.9
t_{max} (hr)	-0.1061	0.1739	4.9167	5.0228	0.9789	0.9203-1.0374	
$t_{1/2}$ (hr)	-0.2592	0.3154	8.8332	9.0924	0.9715	0.9128-1.0302	
λ_z (1/hr)	0.0024	0.0028	0.0843	0.0819	1.0293	0.9721-1.0865	
MRT (hr)	-0.3501	0.3027	13.3390	13.6891	0.9744	0.9370-1.0118	

C_{max}: Maximum concentration, **AUC_{0-t_{last}}**: area under the plasma concentration-time curve from zero to the last measurable concentration, **AUC_{0-∞}**: area under the plasma concentration-time curve from zero up to the infinity, **t_{max}**: time to reach the maximal concentration, **t_{1/2}**: terminal half-life, **λ_z**: elimination rate constant, **MRT**: mean residence time, **CI**: confidence interval.

was for reasons considered by the investigators to be related to the study medication. The incidence of AEs was not significantly different between two formulations.

CONCLUSION

The newly developed SR tablet containing etodolac did not significantly differ in pharmacokinetic profiles compared with the conventional tablet containing etodolac 600 mg. The new SR formulation met the criterion of assumed bioequivalence with the reference products (Lodine SR tablets 600 mg). Both formulations were well tolerated in the studies, with no serious AEs reported. These results indicate that the new SR formulation can be used interchangeably with the conventional formulations. According to the European Guideline on the Investigation of Bioequivalence it is therefore concluded that test formulation is bioequivalent to the corresponding reference formulations.

*This study was sponsored by Nobel Ilac.



C	ORRESPONDING AUTHOR: Seda Ünsalan Saray Mah. Dr. Adnan Büyükdenez Cad. No:14 Ümraniye 34768 İstanbul, seda.unsalan@nobel.com.tr
✓	DELIVERING DATE: 09 / 09 / 2015 • ACCEPTED DATE: 08 / 12 / 2015

REFERENCES

- Jones RA. Etodolac: An overview of a selective COX-2 inhibitor. *Inflammopharmacology* 1999; 7: 269-275.
- Bennett A and Tavares IA. COX-2 inhibitors compared and contrasted. *Expert Opin. Pharmacother* 2001; 2: 1859-1876.
- Liang TH and Hsu PN. Double-blind, randomised, comparative trial of etodolac SR versus diclofenac in the treatment of osteoarthritis of the knee. *Curr Med Res Opin* 2003; 19: 336-341.
- Yılmaz H, Gürel S and Ödemir O. The use and safety profile of non-steroidal antiinflammatory drugs among Turkish patients with osteoarthritis. *Turk J Gastroenterol* 2005; 16: 138-142.
- Benet LZ. Pharmacokinetics of sustained-release etodolac. *Rheumatol Int* 1993; 13: 3-5.
- Dreiser RL. A comparison of the efficacy of etodolac SR (Lodine SR) and etodolac (Lodine) in patients with rheumatoid arthritis or osteoarthritis. *Rheumatol Int* 1993; 13: 13-18.
- Schattenkirchner M. The safety profile of sustained release etodolac. *Rheumatol Int* 1993; 13: 31-35.
- World Medical Association Declaration of Helsinki. Fortaleza, 2013
- Farmasotik Müstahzarların Biyoyararlanım ve Biyoşdeğerliğin Değerlendirilmesi Hakkında Yönetmelik. T.C. Sağlık Bakanlığı ilac ve Eczacılık Genel Müdürlüğü, Ankara, 27.05.1994.
- Guideline on the investigation of bioequivalence: CPMP/QWP/ EWP/1401198 Rev. 1 Corr., London, EMEA, 20 January 2010.
- Guideline for Good Clinical Practice. ICH Harmonised Tripartite Guideline E6, July 2002
- GLP Principles of Good Laboratory Practice as specified by international (OECD- Paris 1998; Directive 2004/10/EC of the European Parliament and of the Council of 11 Feb 2004).
- FDA-Guidance for Industry Bioanalytical Method Validation, U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), May 2001.
- Guideline on bioanalytical method validation (EMA/CHMP/ EWP/192217/2009), July 2011.
- Fast DM, Kelley M, Viswanathan CT et al. AAPS workshop on current topics in GLP bioanalysis: assay reproducibility for incurred samples; *AAPS Journal* 2009; 11: 238-241.
- Shah VP, Kamal K, Midha KK, et al. Bioanalytical method validation- a revisit with a decade of progress (Conference report). *Pharm Res* 2000; 17: 1551-1557.
- Grubbs FE. Procedures for detecting outlying observations in samples. *Technometrics* 1969; 11: 1-21.