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Bioequivalence Study of Acemetacin Tablets

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Abstract: Background and Objective: Acemetacin is a nonsteroidal anti-inflammatory drug (NSAID) structurally derived as a glycolic acid ester of indomethacin, exerting its pharmacological activity through both acemetacin and its primary metabolite, indomethacin. It is indicated for the management of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis, acute musculoskeletal pain, postoperative pain, and dysmenorrhea. The objective of this study was to evaluate and establish the bioequivalence of Acetudil 90 mg Extended Release Capsules (Test; Santa Farma İlaç San. A.Ş, Turkey) with Rantudil® Retard 90 mg Extended Release Capsules (Reference; MEDA Pharma İlaç San. Ve Tic. Ltd. Şti, Turkey) in healthy adult human subjects under fed conditions. **Methods:** This was an open-label, balanced, randomized, two-treatment, two-sequence, four-period, single-dose, fully replicate crossover bioequivalence study conducted under fed conditions in healthy adult male and/or non-pregnant, non-breastfeeding female volunteers aged 18 to 45 years with a BMI of 18.50–29.99 kg/m^2. A total of 48 subjects were enrolled, of whom 47 completed the study. A single oral dose of the test or reference product was administered as per the randomization schedule, and serial blood samples were collected over 18 hours post-dose. Plasma concentrations of acemetacin were determined using a validated LC-MS/MS analytical method. Pharmacokinetic parameters were computed using Phoenix® WinNonlin v8.1, and statistical analysis was performed on ln-transformed pharmacokinetic parameters using SAS® v9.4. The primary pharmacokinetic parameters assessed were Cmax and AUC_{0-t}. Bioequivalence was concluded if the 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) of the test to reference product for both Cmax and AUC_{0-t} fell within the pre-specified acceptance range of 80.00–125.00%. **Results:** The geometric mean ratio (Test/Reference) for ln-transformed Cmax was 95.03% with a 90% CI of 84.51%–106.84%, and for ln-transformed AUC_{0-t} was 98.96% with a 90% CI of 94.47%–103.65%, both falling within the pre-defined bioequivalence acceptance criteria of 80.00–125.00%. The intra-subject coefficient of variation (%CV) for Cmax was 44.83% (R vs R) and 46.78% (T vs R), while for AUC_{0-t} it was 16.83% (R vs R) and 17.74% (T vs R). Both products were well tolerated; only one non-serious adverse event was reported following administration of the reference product, and no serious adverse events were reported during the conduct of the study. **Conclusion:** Bioequivalence was successfully demonstrated between Acetudil 90 mg Extended Release Capsules (Test) and Rantudil® Retard 90 mg Extended Release Capsules (Reference) in healthy adult human subjects under fed conditions, with both primary pharmacokinetic parameters meeting the regulatory acceptance criteria. Both formulations were found to be safe and well tolerated at the administered dose.

Keywords: Acemetacin, Bioequivalence, Extended Release Capsules, Pharmacokinetics, LC-MS/MS, Crossover Study, Fed Condition, NSAID

INTRODUCTION

Acemetacin is a nonsteroidal anti-inflammatory drug with the glycolic acid ester structure of indomethacin.

Its pharmacological activity is due to both acemetacin and its main metabolite indomethacin. Acemetacin is used in the treatment of musculoskeletal and joint disorders and postoperative pain and inflammation.

Acetudil 90 mg Capsul, developed and produced by Santa Farma, is indicated for the treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, as well as acute gouty arthritis, acute musculoskeletal pain, postoperative pain and dysmenorrhea.

MATERIALS AND METHODS

The study design was an open label, balanced, randomized, two treatments, two sequences, four periods, single dose, fully replicate, crossover bioequivalence study under fed condition. Study subjects were screened and enrolled in the study as per the IEC approved protocol. The study was conducted in the age group of 18 to 45 years who met the study eligibility criteria. The study was conducted with orally administered tablets. Blood samples were collected up to 18 hours. These samples were used for measurement of pharmacokinetic parameters of both the products.

Safety evaluation was done by assessing clinical examinations, vital signs assessments, clinical laboratory parameters, and monitoring the subject's wellbeing, symptoms and signs for adverse events. A validated LC-MS/ MS method was used to determine the plasma concentrations of Acemetacin.

Volunteer

Inclusion criteria for this study were:

- Healthy male and/or non-pregnant, non-breast feeding female literate volunteers of 18 to 45 years (both years inclusive) with BMI of 18.50 - 29.99 Kg/m2 and weight > 50 Kg.
- Non-Vegetarian
- Healthy volunteers as evaluated by medical history, vitals and general clinical examination
- Normal or clinically insignificant biochemical, hematological, urine and serology parameters
- Normal or clinically insignificant ECG.
- Negative urine test for drugs of abuse for both males and females; negative pregnancy test for females and do not plan to become pregnant during course of the study and for 03 months after completion of study.
- Volunteers who are willing to use acceptable methods of contraception.

- Volunteers who can give written informed consent and communicate effectively.

Exclusion criteria for this study were:

- History of any major surgical procedure in the past 03 months.
- History of any clinically significant cardiac, gastrointestinal, respiratory, hepatic, renal, endocrine, neurological, metabolic, psychiatric and hematological disorders.
- History of chronic alcoholism/ chronic smoking/ drug of abuse.
- Volunteers with hypersensitivity to Acemetacin or any of the excipients.
- History of consumption of tobacco containing products within 48 hours prior to proposed time of dosing.

Volunteers who are positive for hepatitis B surface antigen, anti-hepatitis C antibody, rapid plasma reagin and human immunodeficiency virus (HIV 1&2) antibodies.

- Present or past history of intake of drugs or any prescription drug or over the counter (OTC) drugs within 14 days which potentially modify kinetics / dynamics of Acemetacin or any other medication judged to be clinically significant by the investigator.
- History of consumption of grapefruit and/or its products within 10 days prior to the start of study.
- Volunteers who had participated in any other clinical study or who had bled during the last 03 months before check-in.
- History of consumption of one or more of the below, 48 hours prior to dosing: Xanthine containing food or drinks such as cola, chocolate, coffee or tea, citrus fruits or items (lime, lemon and orange), alcohol and any other food/beverage known to have interactions as deemed by the investigator.
- Volunteers who are dysphagic.

Study Design

An open label, balanced, randomized, two treatments, two sequences, four periods, single dose, fully replicate, crossover bioequivalence study. Study subjects received tablet per the randomization schedule (Figure 1).

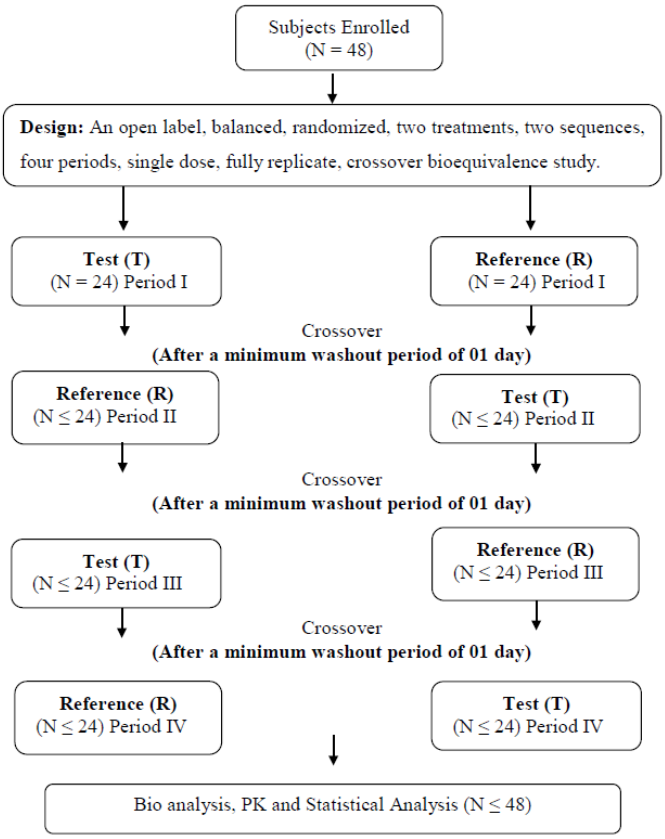

Figure 1: Study design.

Drug Administration

A single oral dose of Test product (T) or Reference product (R) will be administered to study subjects in sitting posture at fixed time with 240 ± 02 mL of water. The order of receiving test and reference products will be followed as per randomization schedule.

Subjects will be instructed not to chew or crush the drug product but to consume it as a whole mouth and hands check will be performed, immediately after drug administration to assess compliance to dosing.

Blood Sampling

00.00 (Pre dose), 01.00, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 05.50, 06.00, 06.50, 07.00, 07.50, 08.00, 08.50, 09.00, 09.50, 10.00, 10.50, 11.00, 12.00, 14.00 and 18.00 hours post dose (Total of 24 samples - 03 mL each). All the blood samples will be collected in the clinic.

Analytical Method

Validated LC-MS/MS method will be used for estimation of Acemetacin in plasma.

Bio-analytical method validation will be done as per EMA Bio-analytical Method Validation guidance, with evaluation for Specificity, Sensitivity, Precision and Accuracy, Stability, Recovery and Dilution Integrity. Subject samples will be analyzed using these

validated methods. Samples of subjects who complete the study will be considered for analysis.

Pharmacokinetic Parameters and Statistical Analysis

Pharmacokinetic analysis will be done using Phoenix® WinNonlin v 8.1.

Primary PK parameters: C_{max} and AUC_{0-t}

Secondary PK parameters: $AUC_{0-\infty}$, T_{max}, $t_{½}$, Kel and $AUC_{\_\%Extrap\_Obs}$

Statistical analysis will be performed on the Ln-transformed pharmacokinetic parameters using SAS® v 9.4. The analysis will include data from subjects who complete the study. If there are drop outs, no replacement will be done.

Safety Analysis

Safety was assessed from the screening period to the end of the study through clinical examinations, vital signs assessment, 12-lead Electrocardiogram (ECG), clinical laboratory parameters (e.g. Haematology, Biochemistry, Urine analysis and Serology test) and monitoring subjects' well-being, symptoms and signs for adverse events.

RESULTS

Pharmacokinetics and Statistics

In the present study, 48 subjects participated, 47 subjects completed the study. The concentrations of 47 subjects were subjected to pharmacokinetic and statistical analysis. The plasma concentration vs. time curve of both the products is presented in (Figure 2).

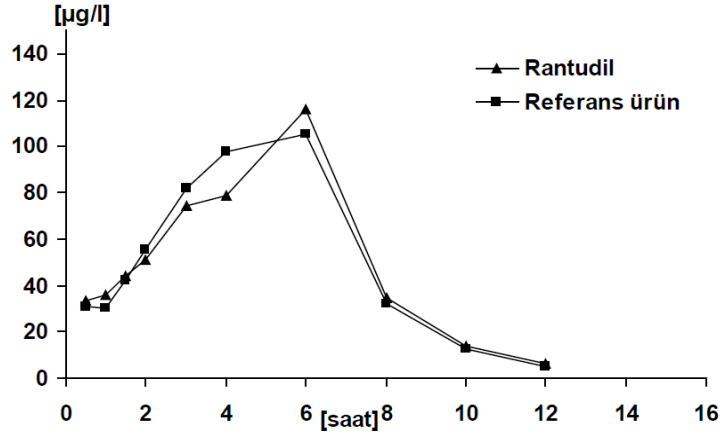

Figure 2: Concentration vs time points of Acemetacin

Brief Summary of Adverse Events

All the subjects were assessed for their well-being throughout the conduct of the study. There was one non-serious adverse event experienced by 01 subject (S18) following

administration of reference product. No serious adverse events were reported during the conduct of this study. Thus, it could be considered that both the test and reference products were well tolerated at the selected dose levels in the selected study population.

The geometric mean ratios, 90% CI, and power of variation of both the products for Ln transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Acemetacin are presented in Table 1 includes the pharmacokinetics of Acemetacin after oral administration.

Table 1: The geometric mean ratios, 90% CIs, power and intra-subject coefficient of variation of tablet for Ln transformed pharmacokinetic parameters Cmax and AUC_{0-t} for Acemetacin are presented below.

Pharmacokinetic Parameters	Test Geometric Mean	Reference Geometric Mean	Test/Reference Ratio	90% Confidence Interval for Test vs. Reference	Power of ANOVA	Intra subject CV (%) R vs R	Intra subject CV (%) T vs R
Ln (C_{max})	328.3144	345.4999	95.03	84.51% - 106.84%	92.52	44.83	46.78
Ln (AUC_{0-t})	1151.2031	1163.3456	98.96	94.47% - 103.65%	100.00	16.83	17.74

CONCLUSION

Bioequivalence was demonstrated between Acemetacin 90 mg Retard Capsules of Santa Farma İlaç San. A.Ş, Turkey and Rantudil® retard (Acemetacin) 90 mg Extended Release Capsules of MEDA Pharma İlaç San. Ve Tic. Ltd. Şti Sarıyer / Istanbul, Turkey in healthy, adult, human subjects under fed condition.

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The authors also acknowledge the Institutional Ethics Committee for their review and approval of the study protocol and for their continued oversight in safeguarding participant welfare.

This study was conducted in accordance with the principles of the Declaration of Helsinki and applicable regulatory guidelines.

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