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Bioequivalence Study of Phenyramidol Tablets

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Abstract: Phenyramidol is a benzyl alcohol derivative with central muscle relaxant and analgesic properties, used in the symptomatic treatment of acute painful muscle spasms associated with musculoskeletal conditions. This study aimed to evaluate the bioequivalence of a test formulation, Draxol® (Phenyramidol HCl 400 mg film-coated tablets, Santa Farma İlaç San. A.Ş., Turkey), against the reference product, Cabral® (Phenyramidol HCl 400 mg film-coated tablets, Recordati İlaç San.), under fed conditions. An open-label, randomized, two-treatment, three-sequence, three-period, single-dose, semi-replicate crossover design was employed in 42 healthy adult volunteers aged 20–45 years. A validated LC-MS/MS method was used to quantify plasma Phenyramidol concentrations across 21 sampling time points over 24 hours post-dose. Primary pharmacokinetic parameters — Cmax and AUC_{0-t} — were analyzed using Phoenix® WinNonlin v7.0, with statistical comparisons performed using SAS® v9.4. Of 42 enrolled subjects, 37 completed the study and 35 were included in the statistical analysis. The geometric mean Test/Reference ratios were 104.97% for Cmax and 100.12% for AUC_{0-t}, with 90% confidence intervals of 84.70–130.09% and 82.48–121.54%, respectively. No serious adverse events were reported, and both formulations were well tolerated. Bioequivalence was successfully demonstrated between the test and reference products, supporting the therapeutic interchangeability of Draxol® and Cabral® in clinical practice.

Keywords: Phenyramidol, bioequivalence, muscle relaxant, analgesic, pharmacokinetics, Cmax, AUC, LC-MS/MS, crossover study, musculoskeletal, film-coated tablet, fed conditions, Santa Farma, Cabral, Draxol.

INTRODUCTION

Phenyramidol was first described pharmacologically in 1959 and is used in the treatment of painful musculoskeletal diseases.

Phenyramidol is a benzyl alcohol derivative that has a central muscle relaxant effect as well as an analgesic effect. It is used as a myorelaxant and analgesic in the treatment of acute and chronic pain in striated muscles and other structures of the locomotor system.

Centrally acting muscle relaxants reduce the increased tone of striated muscles through their effects on the central nervous system and provide relaxation of muscles in spasm. Phenyramidol shows its central muscle relaxant effect by inhibiting the interneurons located on the polysynaptic reflex pathways in the spinal cord.

Draxol 400 mg Film-coated Tablet, developed and produced by Santa Farma, is indicated for the symptomatic treatment of acute painful muscle spasms associated with the musculoskeletal system.

MATERIALS AND METHODS

The study design was an open label, randomized, two treatment, three sequence, three period, single dose, semi replicate, cross over, bioequivalence study under fed conditions. Study subjects were screened and enrolled in the study as per the IEC approved protocol.

The study was conducted in the age group of 20 to 45 years who met the study eligibility criteria. The study was conducted with orally administered tablets. Blood samples were collected up to 24 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 Phenyramidol.

Volunteers

Inclusion criteria for this study were:

- Healthy male and/or non-pregnant, Non vegetarian literate volunteers of 20 to 45 years (both years inclusive) with BMI of 18.50 – 30.00 Kg/m2.
- Healthy volunteers as evaluated by medical history, vitals, general clinical examination and laboratory assessments
- Normal or clinically insignificant biochemical, hematological, urine and serology parameters.
- Normal or clinically insignificant ECG.
- Negative urine test for drugs of abuse, alcohol breath analysis for both males and females and negative pregnancy tests for females.
- Subjects who are willing to practice acceptable methods of contraception.
- Volunteers who can give written informed consent form and communicate effectively.

Exclusion criteria for this study were:

- History of any major surgical procedure in the past 3 months.
- History of any clinically significant cardiac, gastrointestinal, respiratory, hepatic, renal, endocrine, neurological, metabolic, psychiatric, hematological diseases.
- History of chronic alcoholism/chronic smoking/drug abuse
- Known hypersensitivity to any xenobiotic.
- Subject who consumed tobacco containing products within 48 hours prior to proposed time of dosing.
- Present or past history of intake of drugs or any prescription drug or over the counter (OTC) drugs within 7 days which potentially modify kinetics / dynamics of

Phenyramidol or any other medication judged to be clinically significant by the investigator.

- Consumption of grapefruit and/or its products within 10 days prior to the start of study.
- Subject who had participated in any other clinical study or who had bled during the last 3 months.
- Subjects who consume any xanthine containing food or drinks, citrus fruits and allied food (lime, lemon, orange and pomelo), alcoholic beverages and carbonated drinks such as cola during the stay in clinic and within 24 hours prior to dosing.
- Volunteers who are dysphagic.

Study Design

An open label, randomized, two treatment, three sequence, three period, single dose, semi replicate, cross over, bioequivalence study of Phenyramidol HCL 400 mg film coated tablets of Santa Farma İlaç San. A.Ş, Turkey and Cabral® (Phenyramidol HCL) 400 mg film coated tablets of Recordati İlaç San in healthy, adult, human, subjects under fed conditions.

Study subjects received tablet per the randomization schedule (Figure 1).

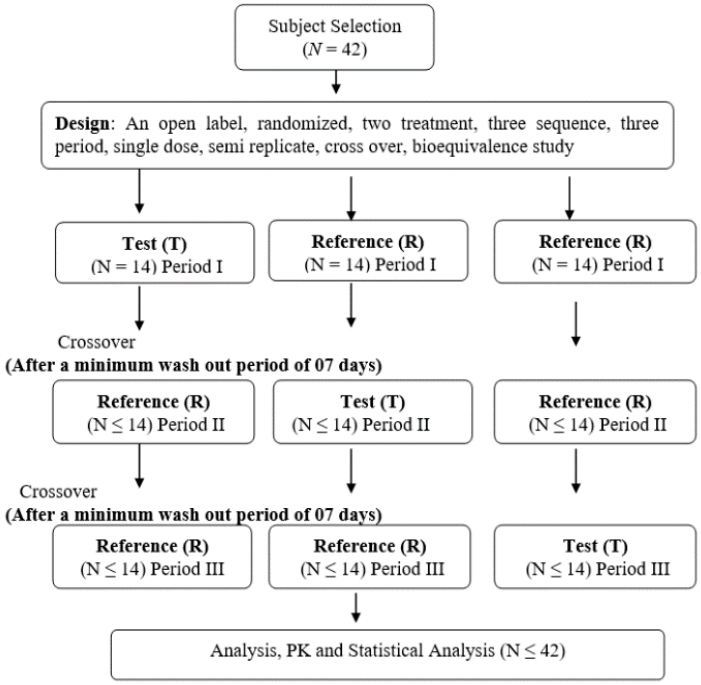

Figure 1: Study design.

Drug Administration

A single oral dose of test (T) or reference product (R) will be administered to study subjects in sitting posture at fixed time points with 240 ± 02 ml of water, at ambient

temperature in each period as per randomization schedule. This activity will be followed by a mouth check to assess compliance to dosing.

Blood Sampling

00.00 (Pre dose), 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.00, 02.25, 02.50, 02.75, 03.00, 03.50, 04.00, 06.00, 08.00, 10.00, 12.00, 16.00 and 24.00 hours post dose (Total of 21 samples-04 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 Phenyramidol 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 7.0.

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

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

Statistical analysis will be performed on the pharmacokinetic parameters using SAS® v 9.4.

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, 42 subjects participated, 37 subjects completed the study. The pharmacokinetic analysis of Phenyramidol was performed using the concentration data obtained from 37 subjects. Statistical analysis of Phenyramidol was performed using the concentration data obtained from 35 subjects.

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

Table 1: The geometric mean ratios, 90% CIs, power and inter-subject coefficient of variation of tablet for Ln transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Phenyramidol are presented above.

Pharmacokinetic Parameters	Test Geometric Mean	Reference Geometric Mean	Test/Reference Ratio	90% Confidence Interval for Test vs. Reference	Lower BE Limit	Upper BE Limit	Intra subject CV (%)	Power of ANOVA
C_{max}	473.2565	450.8349	104.97	84.70% - 130.09%	69.84%	143.19%	68.51	51.68
AUC_{0-t}	882.7215	881.6499	100.12	82.48% - 121.54%	80.00%	125.00%	60.75	58.94

Brief Summary of Adverse Events

All the subjects were assessed for their well-being throughout the conduct of the study. There were 11 adverse events experienced by 09 subjects, 05 adverse events following administration of reference product, 04 with test product and two post study adverse events for 02 subjects. No serious adverse events were reported during the conduct of this study. Both the test and reference products were well tolerated.

CONCLUSION

Bioequivalence was demonstrated between Phenyramidol HCL 400 mg film coated tablets of Santa Farma İlaç San. A.Ş, Turkey and Cabral® (Phenyramidol HCL) 400 mg film coated tablets of Recordati İlaç San in healthy, adult, human, subjects under fed condition.

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The authors further acknowledge the Institutional Ethics Committee for their thorough review and approval of the study protocol, and for their continued oversight in ensuring the safety and well-being of all study participants.

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

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