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Comparative bioavailability of a newly developed irbesartan 300 mg containing preparation

Andrey D. Petrov[1], Emil M. Gatchev[1], Krasimir B. Kalinov[2], Elena P. Filipova[3], Katya H. Uzunova[3], Toni Y. Vekov[4]

[1] Medical University of Sofia, Department of Clinical Pharmacology and Therapeutics, University Hospital "Tsaritsa Yoanna-ISUL", Sofia, Bulgaria
[2] New Bulgarian University, Sofia, Bulgaria
[3] Tchaikapharma High Quality Medicines Inc., Science Department, Sofia, Bulgaria
[4] Medical University- Pleven, Faculty of Pharmacology, Pleven, Bulgaria

SUMMARY

Introduction: Irbesartan (CAS registry: 138402-11-6) is a potent, orally active, selective antagonist of the angiotensin II receptors (type AT1) indicated for the treatment of arterial hypertension and chronic heart failure.

Aim: The objective of the present study was to demonstrate the bioequivalence of an oral test preparation (Irbesartan 300 mg film-coated tablets Tchaikapharma High Quality Medicines Inc., Bulgaria) and a reference (Aprovel 300 mg film-coated tablets, Sanofi Clir SNC, France), by comparing the rate and extent of absorption of both products upon a single oral administration of the tablets under fasting conditions in healthy volunteers.

Methodology: The study was carried out as a single-center, open-label, randomised, two-period, single dose, crossover oral bioequivalence study in 40 healthy male and female subjects under fasting conditions. During each study period blood samples for analysis of irbesartan were taken prior to dosing and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours after dosing. The separated plasma was analyzed in the bioanalytical division of Anapharm Europe with a validated method using reversed phase high performance liquid chromatography coupled to a tandem mass spectrometry detector (RP-LC/MS/MS).

Results: The point estimates with 90% confidence intervals of the geometric mean ratios of test and reference (T/R) in the study were found to be 102.39% (95.55% - 109.71%) for Cmax and 98.56 % (92.72 % - 104.76 %) for AUC0-72. Thus, the corresponding ratios of Cmax and AUC0-72 met the predetermined criteria for bioequivalence (90% confidence intervals of the geometric mean ratios of test and reference within the 80.00% - 125.00%). Both products were generally very well tolerated.

Conclusions: Irbesartan 300 mg film-coated tablets, Tchaikapharma High Quality Medicines Inc., Bulgaria) and Aprovel 300 mg film-coated tablets (Sanofi Clir SNC, France), are bioequivalent with regard to the rate and extent of absorption.

Keywords: irbesartan, bioequivalence, healthy volunteers

Corresponding author:
Andrey D. Petrov, MD, PhD
Specialist in Clinical Pharmacology
Medical University of Sofia, Department of Clinical Pharmacology and Therapeutics, University Hospital "Tsaritsa Yoanna-ISUL", Sofia, Bulgaria
E-mail: andro_p06@yahoo.com

INTRODUCTION

Arterial hypertension is a disease with significant clinical and socio-economic consequences. Globally cardiovascular diseases account for approximately 17 million deaths per year. More than a half of these cases are due to complications resulting from arterial hypertension. It has been estimated that hypertension is responsible for at least 45% of deaths due to stroke and 51% of deaths due to myocardial infarction [1]. Most guidelines suggest that diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations [2, 3]. Angiotensin II receptor blockers are drugs with proven efficacy and good safety profile. The main disadvantage of the group is the high cost of the original products. In this regard, the development of high-quality and cost-effective generic formulations from this group is an important prerequisite these drugs to be used for initial mono- or combination therapy of arterial hypertension.

Irbesartan (CAS registry: 138402-11-6) is a potent, orally active, selective antagonist of the angiotensin II receptors (type AT1). After oral administration, irbesartan is well absorbed: studies of absolute bioavailability gave values of approximately 60-80%. Concomitant food intake does not significantly influence the bioavailability of irbesartan. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. Plasma protein binding is approximately 96%, with negligible binding to cellular blood components. Irbesartan is metabolized by the liver via glucuronide conjugation and oxidation. In vitro studies indicate that irbesartan is primarily oxidized by the cytochrome P450, isoenzyme CYP2C9, while isoenzyme CYP3A4 has negligible effect. Irbesartan and its metabolites are eliminated by biliary and renal pathways – 80% and 20%, respectively. The total body and renal clearance are 157 – 176 ml/min and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is one of the longest in the group - 11 - 15 hours [4].

THE AIM

The aim of the present study was to demonstrate the bioequivalence of an oral test preparation (Irbesartan 300 mg film-coated tablets Tchaikapharma High Quality Medicines Inc., Bulgaria) and a reference (Aprovel 300 mg film-coated tablets, Sanofi Clir SNC, France), by comparing the rate and extent of absorption of both products upon a single oral administration of the tablets under fasting conditions in healthy male and female volunteers.

MATERIALS AND METHODS

Investigational medicinal products

Irbesartan 300 mg film-coated tablets, manufactured by Tchaikapharma High Quality Medicines Inc., Bulgaria, batch number 160317 and expiry date 28 February 2019 were used as test formulation (T). Aprovel 300 mg film-coated tablets, manufactured by Sanofi Clir SNC, France, batch number 4T018 and expiry date May 2017 were used as reference formulation (R).

Study design and participants

The study was designed as a single-center, open-label, randomised, two-period, single dose, crossover oral bioequivalence study in healthy male and female subjects under fasting conditions. The two study periods were separated by a 7 days washout period. This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, last revised by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) [5] and that are consistent with the current ICH GCP Guidelines, regulatory requirements of the EMA [6] and relevant National Laws and Regulations [7, 8]. The study with all relevant documents were reviewed and approved by the Ethics Committee (EC) of University Hospital "TsaritsaYoanna-ISUL", Sofia, Bulgaria and by the Bulgarian Drug Agency.

The clinical part of this study was conducted at the Clinic of clinical pharmacology and therapeutics, University Hospital "TsaritsaYoanna-ISUL".

Written informed consent was obtained from each subject before screening procedure. The Informed Consent Form (ICF) detailed the procedures involved in the study (aims, methodology, potential risks, anticipat-

ed benefits, etc.) and the clinical investigators explained these to each volunteer. The subjects were then provided ample time to understand the information presented in the ICF before signing it.

All participants in the study had to be in compliance with the inclusion/exclusion criteria defined in the study protocol. The most important inclusion criteria were as follows: healthy Caucasian subjects of both sexes (male or female non-pregnant, non-breast-feeding, menopausal, surgically sterile or using adequate contraception method), aged between 18 and 55 years, BMI between 19 and 30 kg/m^2, non-smoking or smoking up to 10 cigarettes a day, able not to smoke from entering the clinical center until leaving at the end of the study.

Eligible subjects were selected after passing a clinical screening examination including collection of demographic data, physical examination, laboratory tests, which included hematology, biochemistry, urine analysis, HIV and hepatitis B antibody and hepatitis C antigen tests. In addition medical history of clinically significant current or past diseases, surgical interventions, weight and height measurement, body mass index calculation, vital signs (blood pressure, heart rate and temperature) and ECG were recorded. Urine drug use tests and alcohol breath tests were performed at screening and Day 0. Laboratory safety tests were carried out in a certified local clinical laboratory.

Drug administration and sample collection

The study included a total of 40 male and female healthy volunteers. The subjects were hospitalized in the clinical center at least 14 hours before dosing on Day 0. At the time of admission each subject received a randomization number and was assign to one of two treatment sequences (test-reference or reference-test). The randomization schedule was generated by the programming module Plan of Statistical package SAS® (current version 9). On the morning of Day 1 (administration day), after at least 10 hours fasting period, in accordance with the randomization schedule, one tablet of the test or the reference product was administered to each subject with 240 ml tap water at room temperature in each period. Subjects were instructed not to chew or crush the tablets but to swallow them whole. The dosing procedure was carried out and witnessed by two Investigators. Compliance was assessed by mouth check. Drinking water and food intake were allowed 1 and 4 hours after dosing, respectively.

During each study period, twenty-one (21) blood samples (4 ml each) were collected from a suitable forearm vein into pre-labeled vacutainers with K_2EDTA. Blood samples were taken prior to dosing and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours after dosing. Immediately after collection blood samples were placed on ice (about 4°C) for the period between sampling and centrifugation for plasma separation from the blood cells. After centrifugation in a refrigerating centrifuge, the separated plasma was transferred in pre-labeled polypropylene tubes and stored at the Clinical center at -80 ± 15 °C until transportation to the analytical laboratory.

Determination of irbesartan in human plasma

Determination of irbesartan was performed by the bioanalytical division of Anapharm Europe using the analytical method SOP ANE 5510.00 entitled "Determination of Irbesartan in Human EDTA Plasma over a Concentration Range of 20 to 8000 ng/mL using a LC/MS/MS Method". The analytical method was developed, validated and partially validated at Anapharm Europe. Irbesartan and internal standard were measured by reversed phase high performance liquid chromatography coupled to a tandem mass spectrometry detector (RP-LC/MS/MS).

Safety evaluation

All volunteers were under continuous supervision by qualified medical staff throughout their stay in the clinical facility to ensure safety and wellbeing. All adverse events (AE), independently of their intensity, seriousness and causality to the investigated drugs, were recorded in source data forms and transferred in case report forms of the volunteers.

During both study periods, vital signs (blood pressure and heart rate) of each volunteer were periodically measured. At the end of the trial, participants' safety was monitored by conducting a final examination, including a physical examination, laboratory tests with

hematological and biochemical blood tests, urine analysis, measurement of vital signs (blood pressure, heart rate, temperature) and ECG record.

Pharmacokinetic parameters and statistical analysis

The following parameters were considered as primary parameters in order to determine the bioequivalence between the test product and the reference product:
- C_{max} – Maximum drug concentration;
- AUC_{0-t} – Area under the plasma concentration-time curve from time zero (0) to the time of last measurable concentration, calculated by the linear trapezoidal rule.

The secondary parameter was:
- T_{max}–Time to reach the maximum concentration.

The following additional parametres were also taken into account:
- $AUC_{0-\infty}$– Area under the plasma concentration-time curve from time zero (0) to infinity (∞) (extrapolated), calculated according the relationship: $AUC_{0-\infty} = AUC_{0-t} + C_t/K_{el}$ (C_t was the last non-zero concentration evaluated in the plasma greater than the limit of quantitation (LOQ));
- k_{el}– Elimination rate constant;
- Residual area under the concentration-time curve – calculated as:

$$\text{Res } \% = \frac{AUC0-\infty - AUC0-t}{AUC0-\infty} \times 100$$

- $t_{1/2}$– Terminal elimination half-life, defined as $t_{1/2} = \ln 2/k_{el}$.

The test product was compared to the reference product with respect to the primary pharmacokinetic parameters using an analysis of variance (ANOVA) with sequence, subject (sequence), product and period effects as fixed effects after logarithmic transformation of the data. Bioequivalence of the test and the reference products was assessed by calculating the 90% confidence intervals for estimates of the geometric mean ratios between the primary parameters of the test and reference products in relation to the conventional bioequivalence range of 80.00% to 125.00% [9]. Data listings, descriptive statistics, statistical analysis and graphs of this study were generated using SAS/STAT® and SAS/GRAPH® software.

Based on a bioequivalence range of 80.00% to 125.00% for C_{max} and AUC_{0-t}, a within-subject coefficient of variation (CV%) of 25%, and a "test/reference" mean ratio 0.93, 36 subjects were needed to achieve a power of 80% at an alpha level of 0.05 to show bioequivalence. To account for possible drop-outs/withdrawals additional 4 subjects were included in the study, therefore a total number of forty (40) subjects were enrolled.

RESULTS

Volunteers' characteristics

Summary of the demographic data of the included in the study subjects are presented in table 1. From all 40 volunteers (22 females and 18males) who were randomized in the study, 39 subjects completed both periods of the study (Figure 1). One male volunteer withdrew from the study at his own request after the 12:00 h post dose blood sample in period 2. There were only four samples missing for this subject in the entire study and pharmacokinetic parameters were calculated successfully for both treatment periods. For this reason he was not excluded from the statistical analysis.

Pharmacokinetic parameters and bioequivalence evaluation

The geometric mean plasma concentration-time curves of irbesartan after administration of a single dose from the test or the reference products on fasting conditions in 40 healthy volunteers are shown in figure 2. The semi-log scale mean plasma concentration-time profiles of irbesartan after administration of a single dose from the test or the reference products on fasting conditions in 40 healthy volunteers are shown in figure 3. Means±SD of the C_{max} were 3705.6±1097.7 ng/mL for the test, and 3690.5±1302.3 ng/mL for the refer-

	Age, years	Height, cm	Weight, kg	BMI, kg/m2
Mean	35.28	166.15	69.06	24.92
SD	8.33	8.52	13.02	3.63
Min	20	148	51	19.36
Max	54	182	97	29.61

Table 1. Summarized demographic data of the volunteers

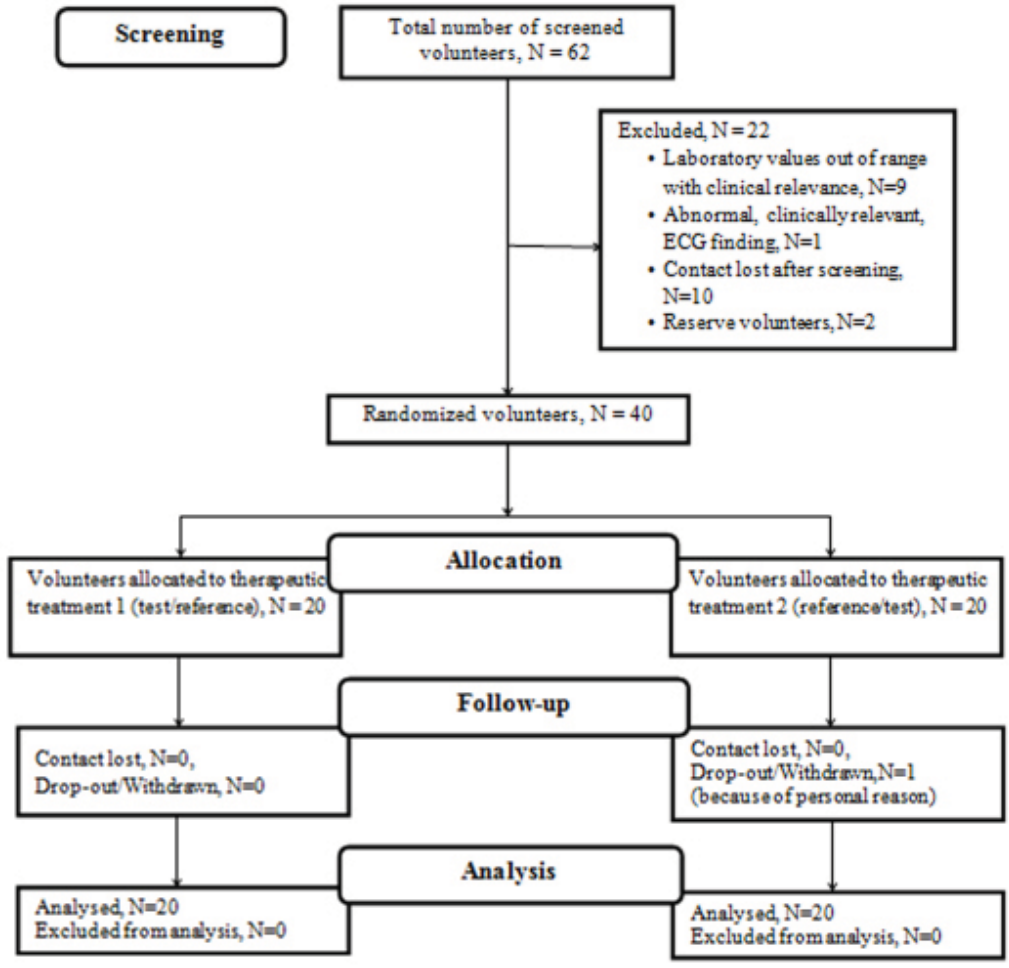

Figure 1. Disposition of the volunteers

ence, respectively. Means±SD of the AUC_{0-72} were: 22102.9±7500.49 for the test and 22596.7±8279.77 for the reference. The values of all investigated pharmacokinetic parameters for irbesartan for the test and the reference products are summarized in table 2.

The point estimates with 90% confidence intervals of the geometric mean ratios of test and reference (T/R) in the study were found to be 102.39% (95.55% - 109.71%) for C_{max} and 98.56 % (92.72 % - 104.76 %) for AUC_{0-72}. Thus, the corresponding ratios of

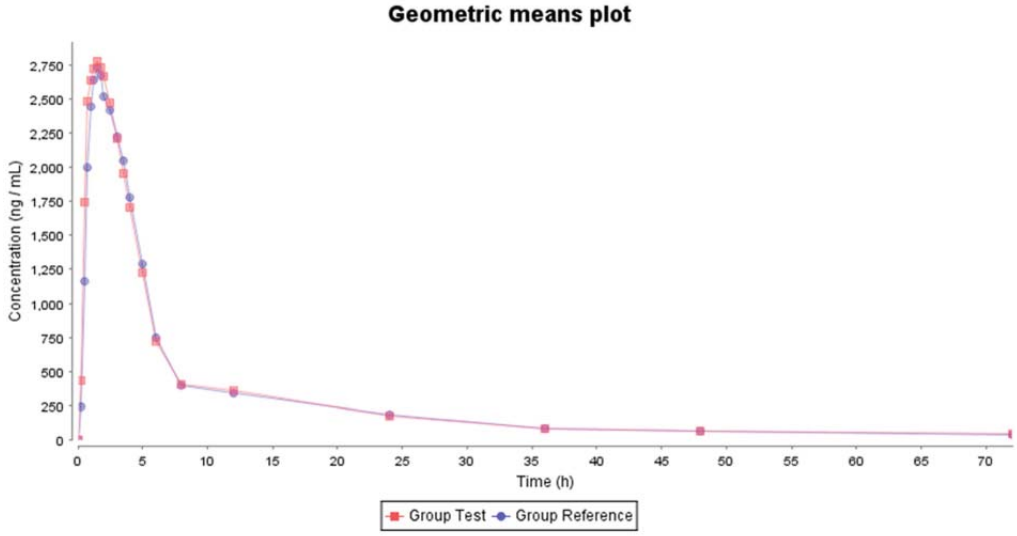

Figure 2. Geometric means plasma concentration-time profiles of irbesartan after intake of a single dose of Irbesartan 300 mg film-coated tablets, manufactured by Tchaikapharma High Quality Medicines Inc., Bulgaria (Test) or Aprovel 300 mg film-coated tablets, manufactured by Sanofi Clir SNC, France (Refence)

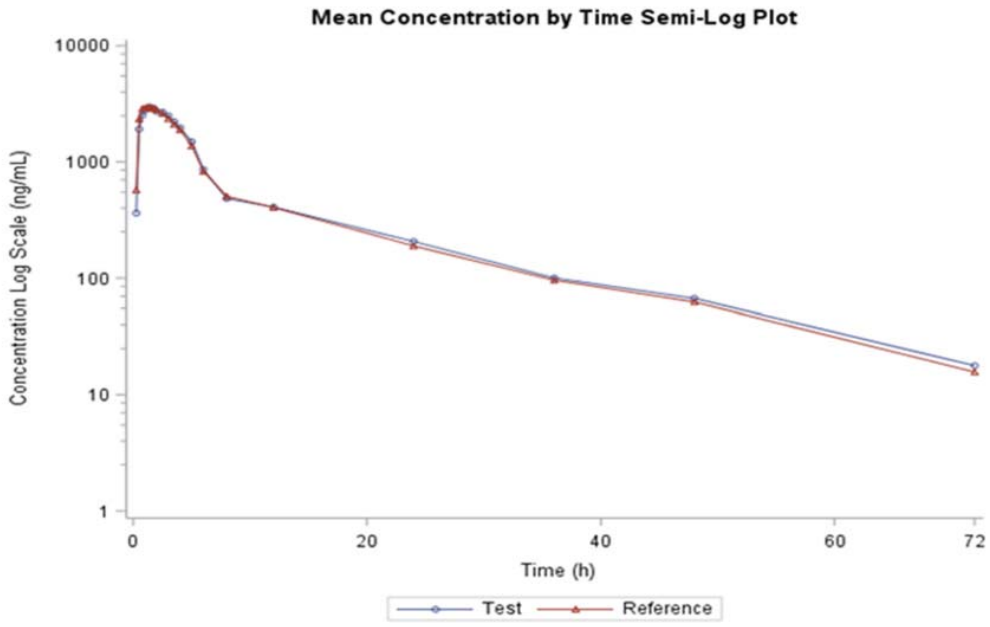

Figure 3. Semi-log scale mean plasma concentration-time profiles of irbesartan after intake of a single dose of Irbesartan 300 mg film-coated tablets, manufactured by Tchaikapharma High Quality Medicines Inc., Bulgaria (Test) or Aprovel 300 mg film-coated tablets, manufactured by Sanofi Clir SNC, France (Refence)

PK parameters	Test product	Reference product
	Mean ± SD	
$C_{max,}$ ng/ml	3705.6 ± 1097.7 [3552.6]	3690.5 ± 1302.3 [3469.8]
AUC_{0-72}, ng.h/ml	22102.9 ± 7500.49 [20897.2]	22596.7 ± 8279.77 [21202.8]
$AUC_{0-\infty}$,ng.h/ml	23295.9 ± 7942.40 [22021.4]	23576.7 ± 8433.79 [22171.8]
$t_{1/2}$, h	14.8 ± 1.08	14.2 ± 6.30
K_{el}, h^{-1}	0.0604 ± 0.0356	0.0585 ± 0.0246
RES_{AUC}, %	4.98 ± 4.77	4.31 ± 3.45
	Median (Range)	
t_{max}, h	1 (0.5 - 5.0)	1.63 (0.5 - 5.00)

Table 2. Summarized pharmacokinetic parameters for irbesartan for Test and Reference products. For C_{max}, AUC_{0-72} and $AUC_{0-\infty}$ in brackets are given geometric means

Cmax and AUC_{0-72} met the predetermined criteria for bioequivalence (90% confidence intervals of the geometric mean ratios of test and reference within the 80.00% - 125.00%) (Table 3).

Safety

Both test and reference products were generally well tolerated after single dose administration. During the study a total of 8 adverse events were reported. There were 3 AEs associated with 3 (7.5%) subjects who received test product: mild headache, moderate headache and mild nausea. All were classified as possibly related to the use of the test drug product. 5 AEs were associated with 3 (7.5%) subjects who received reference product: two cases of mild headache and one mild vertigo were classified as possibly related to the use of the reference drug, while two adverse events of moderate dizziness were assessed as not related to its use. No clinically relevant deviations from medical examination, laboratory tests, measurement of vital signs (blood pressure, heart rate, and temperature) and ECG were observed at final examination. There were no SAEs/SARs (serious adverse events/serious adverse reactions)

Parameter	Pointestimate %	90%CI	Intra- subject CV%	Inter- subject CV%
AUC_{0-72}	98.56	92.72 - 104.76	16.30	32.16
C_{max}	102.39	95.55 - 109.71	18.48	26.07

Table 3. Point estimates of geometric means ratio (%), 90% CI, CV% for primary pharmacokinetic parameters

or SUSARs (suspected unexpected serious adverse reactions) during the study.

DISCUSSION

The market share of generic drugs has grown substantially in recent years. Carrying out bioequivalence clinical trials aims at registering and placing on the pharmaceutical market quality and cost-effective generic drugs, analogues to significantly more expensive reference products, after the expiry of their patent protection.

Key aspects of this study, such as design, choice of the reference product, choice of the volunteers, choice of the dosage of the test and the reference product, duration of blood sampling time, investigated pharmacokinetic characteristics, etc., were in line with current regulatory requirements of the EMA [9] and were consistent with other published data [10, 11, 12].

This study examined the pharmacokinetic properties and bioequivalence of 2 formulations of irbesartan 300 mg tablet in healthy Caucasian male and female subjects. In the present study, the average AUC_{0-72} for all volunteers (except one, dosed with test formulation) was a good representatives of the extent of absorption since the average AUC_{0-72} obtained were found to be greater than 80% of the average AUC_{0-inf} . The point estimate with 90% confidence intervals of the geometric mean ratios of test and reference (T/R) in the study were found to be 102.39% (95.55% - 109.71%) for C_{max} and 98.56 % (92.72 % - 104.76 %) for AUC_{0-72}. The 90% confidence intervals were completely within the predefined bioequivalence criteria of 80.00% to 125.00% for the primary pharmacokinetic parameters of C_{max} and AUC_{0-t}.

CONCLUSION

The results of this study demonstrate that Irbesartan 300 mg film-coated tablets, Tchaikapharma High Quality Medicines Inc., Bulgaria) and Aprovel 300 mg film-coated tablets (Sanofi Clir SNC, France) are bioequivalent with regard to the primary pharmacokinetic parameters - area under the plasma concentration curve from administration to last observed concentration at time (AUC_{0-72}), and the maximum plasma concentration (C_{max}), which provided a strong evidence for marketing authorization of the test formulation.

AKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

The clinical study has been sponsored by Tchaikapharma High Quality Medicines Inc., Bulgaria. Elena Filipova, Katya Uzunova are employees of Tchaikapharma High Quality Medicines Inc., Bulgaria. Andrey Petrov and Emil Gatchev received remuneration by Tchaikapharma High Quality Medicines Inc. for performing the clinical part of the study. Krasimir Kalinov received remuneration by Tchaikapharma High Quality Medicines Inc. for performing the pharmacokinetic and statistical analysis.

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Komparativna bioraspoloživost novog preparata ibersartan 300mg

Andrey D. Petrov[1], Emil M. Gatchev[1], Krasimir B. Kalinov[2], Elena P. Filipova[3], Katya H. Uzunova[3], Toni Y. Vekov[4]

[1] Medicinski univerzitet Sofija, Odeljenje za kliničku farmakologiju i terapiju, Univerzitetska bolnica "Tsaritsa Yoanna-ISUL", Sofia, Bulgaria
[2] Novi Bugarski univerzitet, Sofija, Bugarska
[3] Tchaikapharma High Quality Medicines Inc., Naučno odeljenje, Sofija, Bugarska
[4] Medicinski Univerzitet – Pleven, Fakultet za farmakologiju, Pleven, Bugarska

KRATAK SADRŽAJ

Uvod: Irbesartan (CAS registry: 138402-11-6) je snažan, oralno aktivan, selektivni antagonist angiotenzin II receptora (tip AT1) indikovan za lečenje arterijske hipertenzije i hronične srčane insuficijencije.
Cilj: Cilj ove studije je da pokaže bioekvalenciju oralnog test preparata (*Irbesartan 300 mg film tableta, Tchaikapharma High Quality Medicines Inc., Bugarska*) i referentnog preparata (*Aprovel 300 mg film tableta, Sanofi Clir SNC, Francuska*), upoređivanjem brzine i stepena apsorpcije oba proizvoda nakon pojedinačne oralne administracije tableta kod zdravih dobrovoljaca.
Metodologija: Studija je sprovedena kao unicentrična, otvorena, randomizirana, *two-period*, *single dose*, *crossover oral bioequivalence* studija na 40 zdravih dobrovoljaca muškaraca i žena . Tokom studije radi analize na irbesartan uzorci krvi su uzimani pre doziranja i u 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48 and 72 sata posle doziranja. Izdvojena plazma je analizirana u bioanalitičkom odeljenju Anapharm Evropa validiziranom metodom korišćenjem reverzne faza tečne hromatografije visokih performansi spojene sa tandemom masenog spektrometrijskog detektora (RP-LC / MS / MS).
Rezultati: Utvrđeno je da srednje vrednosti ispitivanja i reference (T/R) u studiji su 102.39% (95.55% - 109.71%) za C_{max} i 98.56 % (92.72 % - 104.76 %) za AUC_{0-72} sa intervalom pouzdanosti od 90%. Stoga, odgovarajući odnos C_{max} i AUC_{0-72} zadovoljavaju predefinisani kriterijum za bioekvivalenciju (za interval pouzdanosti od 90% srednje vrednosti ispitivanja i reference su u intervalu 80.00% - 125.00%). Oba proizvoda su veoma dobro tolerisana.
Zaključak: Irbesartan 300 mg film tablete, (*Tchaikapharma High Quality Medicines Inc., Bulgaria*) i Aprovel 300 mg film tablete (*Sanofi Clir SNC, France*), su ekvivalentne bioraspoloživosti.

Ključne reči: irbesartan, bioekvivalenca, zdravi dobrovoljci

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