BIOEQUIVALENCE STUDY OF A FIXED DOSE COMBINATION OF IRBESARTAN/ AMLODIPINE/HYDROCHLOROTHIAZIDE FILM COATED TABLET MANUFACTURED IN TURKEY

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ABSTRACT

Objective: *The current study was designed to compare the pharmacokinetic properties and tolerability of the newly developed fixed dose combination (FDC) tablet of NOBEL [Irbesartan plus Amlodipine plus Hydrochlorothiazide (HCTZ), Film-coated Tablet, at doses 300 mg/10 mg/12.5 mg], respectively, with those of the conventional tablets of the marketed innovator formulations, CoAprovel 300 mg/12.5 mg Comprimés Pelliculés from Sanofi/Aventis-France and Norvasc 10 mg Tabletten from Pfizer bv Holland, administrated concomitantly in healthy male subjects.*

Material and Method: *36 subjects were randomly assigned into two groups according to a computer-generated randomization scheme. The subjects in group 1 received the reference formulations in period 1 and the test formulation in period 2, and those in group 2 vice versa, with a 21-day washout period between periods 1 and 2. Totally 23 blood sample points were selected including predose. The determination of amlodipine, irbesartan and HCTZ were performed using a validated high performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) in lithium heparinised human plasma.*

Results: *Pharmacokinetic findings showed that the newly developed FDC tablet of Nobel was bioequivalent to the marketed innovator formulations in healthy population under the studied conditions.*

Conclusion: *Results indicated that the new FDC formulation of Nobel can be used interchangeably with the conventional formulations of the innovators.*

Keywords: *Irbesartan, amlodipine, hydrochlorothiazide, bioequivalence, drug combination, hypertension* ***Nobel Med 2014; 10(3): 24-31***

TÜRKİYE'DE ÜRETİLEN İRBESARTAN/ AMLODİPİN/HİDROKLOROTİYAZİD FİLM TABLET SABİT DOZ KOMBİNASYONUNUN BİYOEŞDEĞERLİK ÇALIŞMASI

ÖZET

Amaç: Bu çalışmanın amacı, NOBEL ilaç tarafından yeni geliştirilen sabit doz kombinasyonunun, [Irbesartan/Amlodipin/Hidroklorotiyazid (HCTZ), 300 mg/10 mg/12,5 mg tablet] sağlıklı erkek gönüllülerdeki farmakokinetiği ve tolere edilebilirliğinin inovatörün pazarda mevcut konvansiyonel tabletleri olan CoAprovel 300 mg/12,5 mg Comprimés Pelliculés (from Sanofi/ Aventis-France) ve Norvasc 10 mg Tabletten (from Pfizer bv Holland)'in birlikte uygulanması yoluyla karşılaştırılmasıdır.

Materyal ve Metod: 36 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 21 günlük arınma süresi sonrası, 2. gruptakilere tam tersi olacak şekilde uygulama yapılmıştır. Dozlama öncesi dahil, 23 kan alım noktası seçilmiştir. Lityum heparinli insan plazmasında amlodipin, irbesartan ve HCTZ'nin tayini, valide edilmiş bir tandem mass spektrometre ile birleştirilmiş yüksek basınçlı sıvı kromatografisi (LC-MS/MS) kullanılarak yapılmıştır.

Bulgular: Farmakokinetik bulgular, NOBEL tarafından geliştirilen yeni sabit doz kombinasyonunun, sağlıklı gönüllülerde çalışılan koşullarda pazarda bulunan inovatör formulasyonlara biyoeşdeğer olduğunu göstermiştir.

Sonuç: Bulgular, NOBEL tarafından geliştirilen yeni sabit doz kombinasyon formülasyonunun, tedavide inovatörün konvansiyonel formulasyonları yerine kullanılabileceğini göstermektedir.

Anahtar Kelimeler: İrbesartan, amlodipin, hidroklorotiyazid, biyoeşdeğerlik, ilaç kombinasyonu, hipertansiyon **Nobel Med 2014; 10(3): 24-31**

INTRODUCTION

Antihypertensive therapy can effectively reduce blood pressure (BP), and therefore reduce the risk of coronary heart disease, heart failure, cerebrovascular disease, and may thus prevent mortality. The World Health Organization suggests that people with systolic Blood Pressure ≥140 mmHg and/or diastolic BP ≥90 mmHg should begin treatment, because even low-risk patients with marginally elevated BP are likely to benefit from proper medical intervention.[1]

Angiotensin II (AT) receptor antagonists/blockers represent a relative newer class of antihypertensive agents, developed to overcome some of the deficiencies of ACE inhibitors. Irbesartan (CAS 138402-11-6) is a specific, noncompetitive antagonist of AT_1 receptors, with more than an 8500-fold greater affinity for the AT_1 receptor than for the AT_2 receptor. The oral absorption of irbesartan is well and not affected by food with an average absolute bioavailability of 60-80%. The major circulating metabolite is the inactive irbesartan glucuronide, which accounts for about 6% of the circulating drug [2,3]. Irbesartan is indicated in adults for the treatment of essential hypertension and treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen. Irbesartan, has also been reported to have beneficial effects on glucose/lipid metabolism, by acting as an agonist of peroxisome proliferator-activated receptor (PPAR)-γ, in hypertensive patients with metabolic syndrome.[4,5]

Amlodipine, a third-generation dihydropiridin, is a long-acting L-calcium channel blocker used in the treatment of hypertension and angina pectoris. It exerts its effects by blocking the voltage-dependent L-calcium channels and binding to both dihydropiridin and nondihydropiridin binding sites.[6]

Combination therapy is often required in patients with hypertension, and fixed-dose single-pill combinations have been shown to provide an easier regimen for patients, improving adherence. The efficacy of irbesartan/amlodipine fixed-dose combination treatment for hypertension not adequately controlled with monotherapy with either drug has been investigated in two randomized, open-label (blinded endpoint), multicentre, phase III trials; one (I-ADD) comparing the fixed-dose combination with irbesartan monotherapy (following irbesartan treatment) and the other (I-COMBINE) with amlodipine monotherapy (following amlodipine treatment).[7,8] Data from this study suggest greater efficacy with the fixed-dose combination (FDC) over monotherapy with amlodipine lowering BP after 5 weeks. Both treatment regimens were well tolerated throughout the study (I-COMBINE Study Investigators).[8] →

The association of low-dosed diuretics (e.g. HCTZ) in combination with renin-angiotensin receptor-blocking agents allows maximum benefit from potassium depletion and control of compensatory increase in renin secretion, so increasing the efficacy and safety of renin-angiotensin receptor-blockers. A fixed dose of HCTZ and irbesartan shows additive antihypertensive effect in a dose dependent manner up to HCTZ 25 mg and irbesartan 300 mg with high tolerability in diverse patient groups.[9]

Treatment guidelines note that the combination of an angiotensin receptor blocker (ARB) and a calcium channel blocker (CCB), similar to the combination of an angiotensin-converting enzyme inhibitor (ACEI) or an ARB plus a diuretic provides an effective option for patients with hypertension.[10-12]

The current study was designed to compare the pharmacokinetic properties and tolerability of the newly developed FDC tablet with those of 2 different conventional tablets; amlodipine besylate 10 mg and irbesartan/HCTZ 300/12.5 mg administrated concomitantly in healthy male subjects.

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/m^2 and with no congenital abnormality or chronic disease. Key exclusion criteria included history of hypersensitivity to amlodipine or irbesartan or HCTZ; 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 BP ≤100 mmHg or diastolic BP ≤65 mmHg) or hypertension (systolic BP ≥150 mmHg or diastolic BP ≥100 mmHg); 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 amlodipine or irbesartan or HCTZ; 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 medications.

The Clinical Study Protocol (dated on 04.10.2012), and Informed Consent Form (dated on 04.10.2012) and Case Report Form (CRF) (dated on 04.10.2012) were approved by appointed local ethics committee in Kayseri on 17.10.2012-Decree No: 2012/225 (Local ethics committee in Kayseri is also responsible to approve clinical bioequivalence studies which are going to be conducted in Gaziantep) and by Turkish Medicines & Medical Devices Agency, Republic of Turkey Ministry of Health on 23.11.2012.

This study was performed in accordance with the Declaration of Helsinki and was also in accordance with the relevant laws and regulations of Turkey where the trial was performed, as well as any applicable international guidelines on GCP and GLP. All subjects gave written informed consent before study enrollment.

Drug Products

The following formulations were used:
Test Drug; Irbesartan/Amlodipine/HCTZ 300 mg/10 mg/12.5 mg Film-coated Tablets
Manufacturer: Nobelfarma Ilac Sanayii ve Ticaret A.S, Turkey
Marketing authorisation holder: Nobel Ilac San. ve Tic. A.S.-Turkey
Reference Drug-I; CoAprovel 300 mg/12.5 mg Comprimés Pelliculés
Manufacturer: Sanofi Winthrop Industrie-France
Marketing Authorisation Holder: Sanofi Pharma Bristol/Myers Squibb Snc.-France
Marketing site: Sanofi/Aventis-France
Reference Drug-II; Norvasc 10 mg Tabletten
Manufacturer: Pfizer Manufacturing Deutschland GmbH-Germany
Marketing Authorisation Holder: Pfizer bv-Holland
Marketing site: Pfizer bv-Holland.

Study Design

This was a randomized, open-label, single-dose, 2-way crossover study. 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) will receive one single oral dose of 300 mg irbesartan and 10 mg amlodipine and 12.5 mg HCTZ combination (either one tablet of the test drug or one tablet of CoAprovel 300 mg/12.5 mg Comprimes Pellicules and one tablet of Norvasc 10 mg Tabletten 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 21-day washout period between periods 1 and 2. Study drugs were administered with 240 mL water on the Day 1. The subjects were fasted overnight (at least 10 hours) and administrations 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 that to be taken for the 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 lying in bed. Standard meals containing 1200 kcal were provided for lunch and dinner to both groups at 4 and 10 hours after the dose, respectively.

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 0.33, 0.66 1.00, 1.33, 1.66, 2.00, 2.5, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 11.00, 12.00, 14.00, 16.00, 24.00, 48.00, 72.00 hours after the dose for the test and the reference drugs. Tubes containing blood samples were placed in tube holder in ice-cold water. Blood samples were collected (9 mL each) up to 72 hours for plasma concentration analysis of amlodipine, irbesartan and HCTZ. Before collecting each blood sample, 1 ml of blood was drawn from the catheter and discarded. After each blood sample was drawn, 1 ml of normal saline was injected into the catheter. Separated via centrifugation (3000 rpm for 10 minutes) within 30 minutes after sampling. The plasma was equally divided into two 5 mL transparent, polypropylene tubes (approximately 3 ml per one tube for the irbesartan+HCTZ and approximately 1.5 ml per one tube for the amlodipine analysis). The plasma tubes of each subject were then packed and stored in appropriately labelled tube-racks and stored at -70°C until bioanalysis.

Bioanalysis

A procedure for the quantitative determination of amlodipine, irbesartan and HCTZ in lithium heparinate human plasma using high performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) has been developed and validated at Novagenix Bioanalytical Drug R&D Centre, (Ankara, Turkey) referring to published articles. The analysis samples were prepared with liquid-liquid extraction by using 0.5 and 0.3 ml of human plasma, respectively. The method was validated in a range of 200-8000 pg/ml for amlodipine, 50-8000 ng/ml for irbesartan and 1.5-150 ng/ml for HCTZ. The validation of the assay for irbesartan and HCTZ in human plasma has shown this method to be valid over the range of 200-8000 pg/ml for amlodipine, 1.5-150 ng/ml for HCTZ and 50-8000 ng/ml for irbesartan. Results were found valid in the limit of accuracy and precision 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 (GAMA Tıp Merkezi-G.Antep).

The standard laboratory screening included serum levels of "CBC, glucose, urea, uric acid, creatinine, total bilirubin, sodium, potassium, calcium, creatinin, chloride, SGOT (AST), SGPT (ALT), GGT, alkaline phosphatase, total protein and urinalysis". The blood specimen (12 ml) for the safety laboratory was taken under fasting conditions. Total blood sampling for both laboratory examinations (entry and final) was 24 ml. The volunteers were checked for presence of HBsAg, HCV-Ab and HIV-Ab in serum.

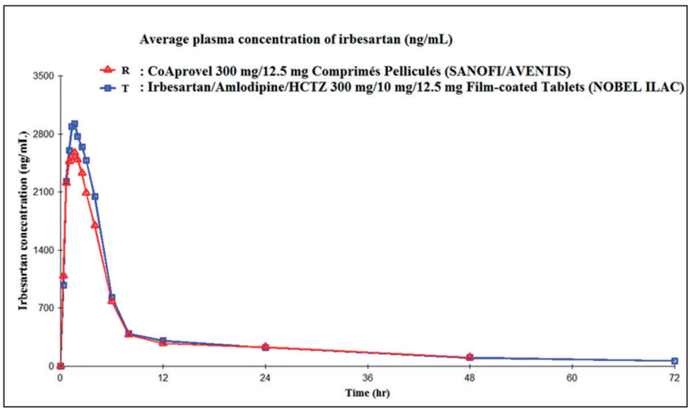
The following parameters were determined in urine (30 mL): pH, protein, glucose (semiquantitatively by means of strip test), ketones, blood, leukocytes, bilirubin, nitrites. If the strip test for any urine parameter was positive, a microscopic examination of the sediment had to be done.

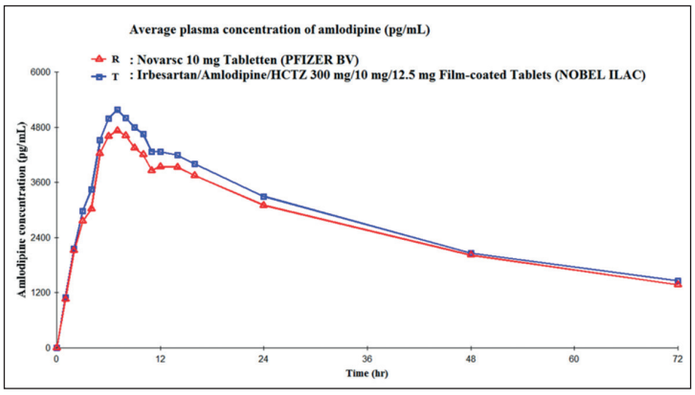
At entry visit and hospitalisation days of period 1 and period 2, the volunteers were requested to provide a urine sample for a drug screen which will include "amphetamines, cannabinoids, benzodiazepines, cocaine, opioids and barbiturates". A list of the normal ranges and units of measurement of the 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 each CRF. 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 conditions each in a randomised manner in two-period with at least 21 days wash-out period. Volunteers were treated under hospitalisation conditions on Day 1 of either period and were hospitalised at the Clinical Facility (FARMAGEN-İKU, Gaziantep) the evening of Day 0 (hospitalisation 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, →

Table 1: Descriptive statistics of demographic data

n* = 36	Age	Weight (kg)	Height (cm)
Mean	24.89	74.00	173.72
SD	7.35	9.15	7.57
Minimum	18	58	160
Maximum	53	92	193
Subject 12**	26	81	185
Subject 16**	20	79	176
Subject 18**	20	80	180
Subject 26**	18	73	180
Subject 29**	20	58	173

*: All subjects were Caucasian male. **: Dropped-out subject





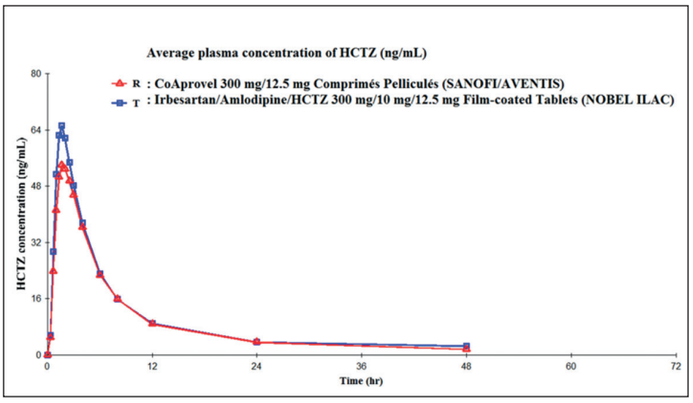


Figure: Average plasma concentrations of irbesartan, amlodipine and HCTZ

drug administration, clinical and other procedures). Adverse events (AEs) were monitored throughout the study. Subsequently, volunteers came to the clinic 3 more times ($t_{24.00}$, $t_{48.00}$, and $t_{72.00}$) per period for blood samples. AEs were monitored throughout the study. 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.

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 volunteeris well-being prior to their discharge from the clinic. If necessary, some volunteers remained at the clinic until any AEs had resolved. 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.

Pharmacokinetic and Statistical Analysis

Pharmacokinetic parameters C_{max} and AUC_{0-72h} of irbesartan, amlodipine and HCTZ were tested for statistically significant differences by means of the Analysis of Variance (ANOVA) test procedure after logarithmic transformation (ln). 90% confidence intervals (two one-sided t-tests) were calculated using WinNonlin Pro (Version 5.3, Pharsight). ANOVA and determination of 90% confidence intervals have been applied to non-logaritmic transformed data of t_{max}, $t_{1/2}$, λz and MRT and to ln transformed data of $AUC_{0-\infty}$.

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_{0-72}) of amlodipine, irbesartan and HCTZ. The 3 drugs were assumed to be bioequivalent, as defined by the Turkish Medicines & Medical Devices Agency, Republic of Turkey Ministry of Health, and international guidelines (ICH, EMA and FDA Guidelines) if 90% CIs for the treatment ratios of the primary parameters were within the range of 0.80 to 1.25. Demographic data of volunteers was shown in Table 1.

RESULTS

Study Subjects

52 subjects were screened. 36 subjects were randomised and included into the study. The subjects were divided into two groups according to the randomisation table. There have been five drop-outs: Before dosing-Period 1: Subject 18 and 29 have →

left with his own decision. In Period 1: Subject 12 (because of vomiting), 16 (did not come to three consecutive blood samplings) and 26 (has left with his own decision).

They have been replaced with Subject 12R, 16R, 18R, 26R and 29R, respectively. Test product administered to 37 subjects (including 1 drop-out subject); Reference product administered to 38 subjects (including 2 drop-out subjects).

After 21 days washout period; in period 2, the subjects have been administered by the other drug that they have not been administered in the period 1. 36 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 irbesartan amlodipine, and HCTZ after the test and the reference drugs are depicted in the Figure, Table 2 and Table 3. 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 to assume bioequivalence of amlodipine, irbesartan and HCTZ yielding 90% CI ratios of 1.0153 to 1.0894, 1.0377 to 1.2012 and 1.0210-1.1704 for AUC0-72 and 1.0372 to 1.1059, 1.0087 to 1.1609 and 1.0481-1.2423 for C_{max}, respectively. In addition, the 90% CIs for the geometric mean ratios of the secondary parametersof amlodipine, irbesartan and HCTZ were 0.9698 to 1.0905, 1.0651 to 1.2577 and 1.0188 to 1.1579 for $AUC_{0-\infty}$, 0.8401 to 1.0365, 0.8503 to 1.8834 and 0.9355 to 1.0863 for $t_{1/2}$, and 0.9144 to 1.1158, 1.0226 to 1.3656 and 0.7880 to 1.0445 for t_{max}, respectively.

When tested at the significance level of 0.05, the sequence effect was not significant in any of the parameters.

Tolerability

The test and the reference drugs were well tolerated in all subjects. For Test Product; Subject 07, 21 (in Period 1) and 32 (in Period 2) had dizziness; Subject 12, 25 and 29R had headache (in Period 1); Subject 12 vomitted (in Period 1, after $t_{10.00}$) and dropped out.

For Reference Product; Subject 03 had sniffles (in Period 1); Subject 13, 22 and 32 had headache (in Period 1); Subject 14 and 28 had dizziness (in Period 1).

All AEs were mild or moderate, with no serious AEs being 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).

Table 2: Pharmacokinetic results

PHARMACOKINETIC RESULTS (AMLODIPINE)		
	Arithmetic Mean ± SD (n=36)	
Parameters (Units)	**Test (T)**	**Reference (R2)**
C_{max} (pg/mL)	5435.321 ± 1332.718	5044.519 ± 1042.014
AUC_{0-72h} (pg.hr/mL)	192562.823 ± 43358.012	183114.944 ± 43201.462
$AUC_{0-\infty}$ (pg.hr/mL)	282727.737± 72276.911	280404.783 ± 102652.706
t_{max} (hr)	7.472 ± 1.594	7.361 ± 2.368
$t_{½}$ (hr)	40.567 ± 9.569	43.236 ± 17.142
λ_z (1/hr)	0.018± 0.004	0.018 ± 0.004
MRT (hr)	60.787 ± 13.189	64.980 ± 24.200
PHARMACOKINETIC RESULTS (IRBESARTAN)		
	Arithmetic Mean ± SD (n=36)	
Parameters (Units)	**Test (T)**	**Reference (R1)**
C_{max} (ng/ml)	3264.396 ± 1007.951	3031.205 ± 965.558
AUC_{0-72h} (ng.hr/mL)	19123.622 ± 6541.422	17420.758 ± 7143.633
$AUC_{0-\infty}$ (ng.hr/mL)	23060.670± 12427.476	19665.853 ± 8427.249
tmax (hr)	1.993± 0.964	1.669 ± 1.037
$t_{½}$ (hr)	14.866 ± 20.483	10.877 ± 7.335
λ_z (1/hr)	0.083 ± 0.053	0.096 ± 0.059
MRT (hr)	16.923 ± 25.914	12.938 ± 6.810
PHARMACOKINETIC RESULTS (HCTZ)		
	Arithmetic Mean ± SD (n=36)	
Parameters (Units)	**Test (T)**	**Reference (R1)**
C_{max} (ng/mL)	69.039 ± 20.250	59.964 ± 15.968
AUC_{0-72h} (ng.hr/mL)	399.570 ± 82.204	369.436 ± 97.021
$AUC_{0-\infty}$ (ng.hr/mL)	440.038± 89.465	408.842 ± 104.600
tmax (hr)	1.686 ± 0.421	1.840 ± 0.677
$t_{½}$ (hr)	7.573 ±1.990	7.491 ± 1.953
λ_z (1/hr)	0.098± 0.027	0.100 ± 0.032
MRT (hr)	9.573 ± 1.975	9.579 ± 1.595

C_{max}: Maximum concentration; **AUC_{0-72h}:** Area under the plasma concentration-time curve from zero up to 72h; **$AUC_{0-tlast}$:** Area under the plasma concentration-time curve from zero to the last measurable concentration; **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: Irbesartan/Amlodipine/HCTZ 300 mg/10 mg/12.5 mg Film-coated Tablets
Reference Drug-I: CoAprovel 300 mg/12.5 mg Comprimés Pelliculés
Reference Drug-II: Norvasc 10 mg Tabletten

DISCUSSION

Following oral administration of irbesartan, peak plasma concentrations are attained at 1.5-2 h for doses up to 600 mg and the terminal elimination half-life is between 11 and 15 h. Amlodipine is well absorbed after oral doses with peak blood concentrations occurring after 6 to 12 hours. It has relatively →

Table 3: Statistcal results

AMLODIPINE							
Parameter	**Difference**	**DiffSE**	**TESTLSM**	**REFLSM**	**Ratio**	**90% CI**	**Intrasubject CV**
$\ln(C_{max})$	0.0686	0.0190	8.5749	8.5063	1.0710	1.0372 - 1.1059	8.1
$\ln(AUC_{0-72h})$	0.0504	0.0208	12.1439	12.0935	1.0517	1.0153 - 1.0894	8.9
$\ln(AUC_{0-\infty})$	0.0280	0.0347	12.5216	12.4936	1.0284	0.9698 - 1.0905	14.8
t_{max}	0.1111	0.4383	7.4722	7.3611	1.0151	0.9144 - 1.1158	
$t_{½}$	-2.6689	2.5109	40.5674	43.2363	0.9383	0.8401 - 1.0365	
λ_z	0.0005	0.0007	0.0181	0.0176	1.0281	0.9591 - 1.0970	
MRT (hr)	-4.1929	3.4589	60.7874	64.9803	0.9355	0.8454 - 1.0255	
IRBESARTAN							
Parameter	**Difference**	**DiffSE**	**TESTLSM**	**REFLSM**	**Ratio**	**90% CI**	**Intrasubject CV**
$\ln(C_{max})$	0.0789	0.0415	8.0471	7.9682	1.0821	1.0087 - 1.1609	17.8
$\ln(AUC_{0-72h})$	0.1102	0.0432	9.8074	9.6972	1.1165	1.0377 - 1.2012	18.5
$\ln(AUC_{0-\infty})$	0.1462	0.0491	9.9590	9.8128	1.1574	1.0651 - 1.2577	21.1
t_{max}	0.3239	0.1692	1.9928	1.6689	1.1941	1.0226 - 1.3656	
$t_{½}$	3.9898	3.3220	14.8663	10.8765	1.3668	0.8503 - 1.8834	
λ_z	-0.0121	0.0095	0.0835	0.0956	0.8731	0.7050 - 1.0413	
MRT	3.9849	4.2323	16.9227	12.9378	1.3080	0.7547 - 1.8613	
HCTZ							
Parameter	**Difference**	**DiffSE**	**TESTLSM**	**REFLSM**	**Ratio**	**90% CI**	**Intrasubject CV**
$\ln(C_{max})$	0.1320	0.0503	4.1905	4.0585	1.1411	1.0481 - 1.2423	21.6
$\ln(AUC_{0-72h})$	0.0891	0.0404	5.9685	5.8795	1.0931	1.0210 - 1.1704	17.3
$\ln(AUC_{0-\infty})$	0.0826	0.0379	6.0652	5.9826	1.0861	1.0188 - 1.1579	16.2
t_{max}	-0.1542	0.1396	1.6861	1.8403	0.9162	0.7880 - 1.0445	
$t_{½}$	0.0818	0.3339	7.5728	7.4910	1.0109	0.9355 - 1.0863	
λ_z	-0.0021	0.0059	0.0978	0.0998	0.9794	0.8790 - 1.0799	
MRT	-0.0054	0.3179	9.5735	9.5789	0.9994	0.9433 - 1.0556	

C_{max}: Maximum concentration; **AUC_{0-72h}:** Area under the plasma concentration-time curve from zero up to 72h; **$AUC_{0-tlast}$:** Area under the plasma concentration-time curve from zero to the last measurable concentration; **t_{max}:** Time to reach the maximal concentration; **$t_{1/2}$:** Terminal half-life; **λ_z:** Elimination rate constant; **MRT:** Mean residence time; **DiffSE:** the estimated treatment difference on the linear scale standard error; **TESTLSM;** The Test Least Square Means; **REFLSM:** Reference Least Square Means; Ratio: TESTLSM/REFLSM; **CI:** Confidence Interval; **CV:** Coefficient of vaiation

long terminal elimination half-life and steady-state plasma concentrations are not achieved until after 7 to 8 days of use. HCTZ is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours. Pharmacodynamic and pharmacokinetic characteristics of these three drugs allow them to be good candidates for triple combination for treatment of hypertension. Because, irrespective of an evidence, to take 3 pills simultaneously, can significantly decrease medication compliance in patients. Therefore, a FDC tablet comprising amlodipine besylate, irbesartan and HCTZ in a single dosage form may be a more efficient treatment option than coadministration of each drug in a separate dose.

Present study aimed to investigate if triple FDC combination of Nobel was bioequivalent to those of innovator products, amlodipine (a single pill) and irbesartan-HCTZ (a single pill as a dual FDC combination) and results showed that the newly developed FDC tablet of amlodipine and irbesartan/HCTZ was bioequivalent to the coadministered reference (CoAprovel 300 mg/12.5 mg Comprimes Pellicules and Norvasc 10 mg Tabletten) product in this healthy population under the fasting 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 was for reasons considered by the investigators to be related to the study medication. The incidence of AEs was not significantly different between the 2 formulations.

CONCLUSION

The newly developed FDC tablet containing amlodipine 10 mg and irbesartan 300 mg and HCTZ 12.5 mg did not significantly differ in pharmacokinetic profiles compared with the conventional tablet containing amlodipine besylate→

10 mg and conventional FDC including irbesartan 300 mg/HCTZ 12.5 mg. The new FDC formulation met the criterion of assumed bioequivalence with the coadministered reference (CoAprovel 300 mg/12.5 mg Comprimes Pellicules and Norvasc 10 mg Tabletten) products. Both formulations were well tolerated in the study, with no serious AEs reported. These results indicate that the new FDC formulation can be used interchangeably with the conventional formulations. According to the European Guideline on the Investigation of Bioequivalence it may be therefore concluded that test formulation is bioequivalent to the corresponding reference formulations. Overall, it was judged that both period of the study were conducted with a good tolerance of the subjects to study drugs.

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