Drug Substance(s) Candesartan Cilexetil, Candesartan (test), Felodipine, Felodipine (test)

Study Code D2452L00021

SYNOPSIS

Date 21 October 2009

Evaluation of the Pharmacokinetic Interaction Between Candesartan and Felodipine in a Combination Package Compared to the Separate Intake of the reference brands Atacand and Splendil after a fasting period.

Study dates	**Phase of development**
First subject enrolled 28 October 2008	Pharmacokinetic Interaction
Last subject completed 13 November 2008	

Objectives

Primary

To evaluate the pharmacokinetic interaction of test formulation of candesartan (16 mg tablet) and felodipine (extended release 5 mg tablet) together in a combination package, comparing with the fasting period intake of commercial formulations of both Atacand® (16 mg tablet) and Splendil® (extended release 5 mg tablet)

Study design

This study consisted in an open label trial, crossover assignment, single-arm pharmacokinetics study, in wich healthy volunteers received 3 treatments in 6 sequences and in 3 periods (Williams' Plan). In each period either tested formulation or the reference formulation was administered, according to an aleatorization test list generated by SAS® PROC PLAN system, version 9.1.3.

Target subject population and sample size

50 Healthy volunteers aging 18 to 50 years

Investigational product and comparators: dosage, mode of administration and batch numbers

Candesartan Cilexetil was supplied in 16 mg simple tablets together with Felodipine, in an extended release 5 mg tablet or one 16 mg simple tablet of Atacand® together with Splendil®, extended release 5 mg tablet, according to the aleatorization plan. Tablets were given to healthy volunteers with 200 mL of pure mineral non-sparkling water.

Batch Numbers:

- Candesartan and felodipine combination packs – Atacand® plus Splendil® - 81234/81211
- Atacand®: 81234

- Splendil®: 81211

Duration of treatment

After entering the hospital, healthy volunteers had their last meal, starting fasting period at 9:00pm in the first day until 5 hours after medication. A ten hours fasting period was placed before the first medication. The followed meal plan was:

- dinner in the night of hospital admission;
- a standard lunch was offered between 5 to 6 hours after medication;
- a standard snack was offered between 7 to 8 hours after medication;
- a standard dinner was offered between 10 to 12 hours after medication;
- a standard supper was offered between 13 to 14 hours after medication;
- a standard breakfast was offered 24 hours after medication;

The volunteers didn't have water from 2 hours before medication until programmed water supply times, in which 200 mL of pure mineral non-sparkling water was offered. After 2 hours of medication ingestion water supply was free.

Variables

- Pharmacokinetic

$AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max}, $t_{½}$, t_{max}, CL/F, Vz/F, in the fed and fasted states.

- Safety

Adverse events, clinical chemistry, haematology, 12-Lead ECG, blood pressure, pulse, sorology (HIV 1 and 2, hepatitis B and C), pregnancy blood test (B HCG).

Statistical methods

Statistical analysis was performed after logarithmic transformation (natural logarithm) and was based upon an aditive model for AUC and C_{max} values. Model value adjustments were not used in statistical evaluation of T_{max}, $T_{1/2}$, Ke, Vz/F and CL/F. The model takes into account sequencing effects, volunteers in the sequence, formulation and period. Specific ratios were calculated for T/R1 and T/R2 ("test" formulation / "reference" formulation 1 and "test" formulation / "reference" formulation 2) to AUC and C_{max}. Bioavailability for test formulation and reference number 1 and 2 was performed by geometric averages estimates with a correspondent confidence interval of 90%. Study formulations were considered equivalent when the confidence interval of geometric average ratios of $AUC_{(0-t)}$ (absorption extension) and C_{max} (absorption velocity) presented into the 80-125% interval for the first parameter and 75-133% for the second one. A broader interval for C_{max} was described for pharmacokinetics interactions. All analysis were performed through the SAS® system, version 9.1.3. Adjusted models were logarithmically transformed. In the case of atypical data or discrepant ones, analysis was repeated with the exclusion of atypical data.

Subject population

A total of 50 healthy volunteers were randomized, male and female, aging from 18 to 50 years and with a body mass index (BMI) between 19 and 28,5 (Dietary Guidelines Advisory Committee, 2005). From the randomization group, 36 subjects were enrolled. Subjects number 04, 15 and 35 were replaced due to absence in the first night of hospitalization. Subjects number 17, 19 and 34 were discontinued from the study. Subject number 17 was exluded from the study during period 2 of hospitalization due to an adverse event. Subject number 19 was excluded before hospitalization in the first period due to absence. Subject number 34 was excluded from study during period 3 of hospitalization, before drug administration, due to absence. The clinical phase of the study ended

with 33 healthy volunteers.

Summary of pharmacokinetic results

- Results for candesartan:

In this pharmacokinetics study, confidence interval (90%) for geometric averages ratios of the formulations T and R1 (candesartan), of $AUC_{(0-t)}$ and C_{max} parameters, the power and coeficient of variation in each individual were:

Parameter	T/R ratio (%)	Lower limit CI (%)	Upper limit CI (%)	Power of test (%)	VC (%)
$AUC_{(0-t)}$ (ng.h/mL)	102.51	90.00	116.77	72.81	32.46
C_{max} (ng/mL)	110.40	93.94	129.74	29.50	40.81

- Results for Felodipine

In this pharmacokinetics study, confidence interval (90%) for geometric averages ratios of the formulations T and R2 (felodipine), of $AUC_{(0-t)}$ and C_{max} parameters, the power and coeficient of variation in each individual were:

Parameter	T/R ratio (%)	Lower limit CI (%)	Upper limit CI (%)	Power of test (%)	VC (%)
$AUC_{(0-t)}$ (ng.h/mL)	102.69	89.46	117.88	99.99	34.46
C_{max} (ng/mL)	96.17	82.07	112.69	99.99	39.95

a. Blood samples were taken before drug administration and at 48 hours after that, in predetermined intervals. 2502 samples were taken in total and preceded to quantification. Plasma concentration of candesartan + felodipine were determined through high-efficiency liquid chromatography together with mass spectrometry in MS/MS mode;

b. For each formulation, a sequence of estimates were made: C_{max}, AUC from medication intake until the last sample in the upper limit of quantification $AUC_{(0-t)}$ and the $AUC_{(0-inf)}$;

c. 33 healthy volunteers were enrolled in the pharmacokinetics evaluation in which estimates for the geometric average ration for tested formulations / reference for Cmax and $AUC_{(0-t)}$ and correspondent 90% confidence interval;

Summary of pharmacodynamic results (not applicable)

No pharmacodynamic variables were measured.

Summary of pharmacokinetic/pharmacodynamic correlations (not applicable)

No pharmacodynamic variables were measured.

Summary of population pharmacokinetics (not applicable)

No population pharmacokinetic analysis was performed.

Summary of pharmacogenetics (not applicable)

No population pharmacogenetics analysis was performed.

Summary of safety results

There were no deaths, SAE or other significant AE during the study

- 58 adverse events occurred in the study period;
    - 24 adverse events were classified as non-study drugs related;
    - 27 adverse events were related to study drugs.
    - Seven events were classified as probably related to study drugs.
- There was no serious adverse event.