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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-437/S-002

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: **21,437 SE1 002**

Submission Dates: April 4, 2003

Drug Name: Inspra (eplerenone)

Applicant: Pharmacia Corp.

Submission: Supplemental NDA

Reviewer: Elena V. Mishina, Ph.D.

B. Nhi Nguyen, Pharm.D.

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2 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I has reviewed the information included in the sNDA 21,437. The Office of Clinical Pharmacology and Biopharmaceutics recommends adopting the proposed language for the labeling.

/S/

Date_____

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

/S/

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

CPB Briefing was held on September 3, 2003

Attendees: Drs. M. Mehta, P. Marroum, J. Hunt, A. Bhattram.

cc list: NDA 21,437, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

3 EXECUTIVE SUMMARY

3.1 Background

Pharmacia is seeking approval of Inspra (Eplerenone), an aldosterone receptor antagonist, for the treatment of heart failure after an acute myocardial infarction. The recommended starting dose is 25 mg once daily which should be titrated to the target dose of 50 mg once daily, preferably within 4 weeks as tolerated by the patient. The original NDA 21-437 was approved for the treatment of hypertension in September 2002. The sponsor cross-referred to NDA 21-437 for clinical pharmacology information regarding metabolism, drug-drug-interaction, and the influence of renal failure and hepatic insufficiency on eplerenone pharmacokinetics.

3.2 Current Submission

This sNDA review evaluates whether the pharmacokinetic of eplerenone in patients with symptomatic heart failure is comparable to that in healthy volunteers and if any dose adjustment is warranted for the CHF patients.
With this supplemental NDA, the sponsor submitted the reports of two clinical pharmacology studies:

"Effect of Chronic Congestive Heart Failure on the Pharmacokinetic of Eplerenone" (NE3-01-02-058) and

"Dose-Ranging Study of Eplerenone vs. Placebo in Patients with Symptomatic Heart Failure" (EPHESUS Study, IE3-99-02-035), population pharmacokinetics sub-study.

The study 058 compares the pharmacokinetics of eplerenone and its metabolites in the 8 CHF patients and in the 8 matched (by gender and age) control subjects after a single 50 mg dose of eplerenone and at steady state (day 7). The plasma sampling was extensive, and noncompartmental methods were used to calculate the pharmacokinetic parameters. The plasma levels of eplerenone, SC-70303 (open-ring form of eplerenone) and SC-71597 (primary inactive metabolite) in CHF patients were higher than in the matched control group. Overall, eplerenone, SC-70303 and SC-71597 AUC and Cmax values increased 38% for eplerenone, 35% for SC-70303 and 30% for SC-71597. The comparison of the pharmacokinetic parameters using ANCOVA has shown that all differences between the CHF patients and the matched control subjects were statistically insignificant. However, the differences may not be recognized as significant due to the very high inter-subject variability and not sufficient sample power. None of these differences were considered clinically important.
A subgroup of patients in the EPHESUS study (035) participated in the pharmacokinetic plasma sampling. About 4 plasma samples were obtained from each patient using a pseudo-random plasma sampling design. The population PK modeling was used to estimate the physiologic pharmacokinetic parameters. A total of 258 patients were enrolled in the population pharmacokinetics substudy and provided 1416 plasma

concentrations, but only data from the 134 eplerenone patients with 726 samples were used to support the pharmacokinetic model. The data were extensively censored due to missing time or concentration values. Additionally, the data from the patients who had large absorption time were excluded from the analysis. The final population model was supported by 113 patients with 324 concentrations. The proper model building routine was employed, and the final model included the effect of SGOT on clearance (CL/F), and the effects of age, body weight and gender on the volume of distribution (V/F).
The sponsor's model estimated clearance as 4.9 L/kg. This value is about twice lower than the clearance values estimated for the group of hypertensive patients and similar with the clearance values for the healthy elderly subjects. In the original NDA, no dose adjustment either for the elderly or for the patients with mild to moderate hepatic impairment, was recommended because the pharmacokinetic differences were not considered as clinically significant.

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4 QUESTION BASED REVIEW

4.1 General Attributes

Was the information about the general attributes of Inspra submitted with this sNDA?

No. The information regarding eplerenone pharmacokinetics, metabolism, drug-drug interactions, and the influence of renal and hepatic impairment on eplerenone pharmacokinetics was included in the original hypertension submission (NDA 21-437).

4.2 Pharmacokinetic Studies in CHF patients

Was the direct comparison of eplerenone pharmacokinetics in CHF patients and in matched control subjects performed?

Yes. The pharmacokinetics of eplerenone and its metabolites after a single 50 mg dose and at steady state (day 7) was performed in 8 CHF patients and 8 matched by age and gender control subjects. The plasma profiles of eplerenone, SC-70303 (open-ring form of eplerenone) and SC-71597 (primary inactive metabolite) in CHF patients were higher than in the matched control group. The pharmacokinetic parameters were calculated by non-compartmental method using the rich data file. Overall, eplerenone, SC-70303 and SC-71597 AUC and Cmax values increased 38% for eplerenone, 35% for SC-70303 and 30% for SC-71597. Figure 1 shows the comparison of eplerenone plasma concentrations after multiple 50 mg daily doses on Day 7.

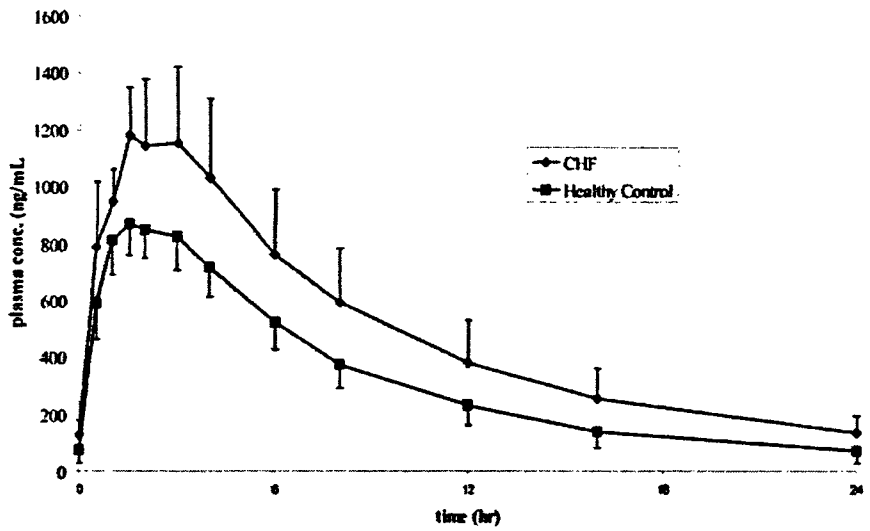

Figure 1. Steady-State Mean (SE) Plasma Concentrations of Eplerenone Following Multiple Once Daily 50 mg Doses in CHF Patients and Healthy Controls

Despite of these differences, the ANCOVA analysis performed by the sponsor concluded that the differences between the calculated pharmacokinetic parameters (AUC0-t, AUC0-∞, Cmax, CL/F, Vss, XU) were not statistically significant for each measured entity (see Appendix).

Were the population pharmacokinetic parameter estimates of eplerenone in CHF patients similar to that obtained in the previous study?

Yes. Sparse plasma samples were obtained from the sub-population of the CHF patients in the clinical Study EPHESUS (035). The sponsor extensively censored the data, using in the final model the data from 113 patients with 324 concentrations from a total of 258 patients enrolled in the sub-study providing 1416 plasma concentrations. The reasons for the data censoring were not always explainable. Not only missing plasma concentrations and dose timing data were deleted from the file but additionally, the data from the patients with long absorption time were deleted.
A one-compartment model with first-order absorption described the pharmacokinetic profile of eplerenone following oral dosing.. The investigated covariates on the key pharmacokinetic parameter, apparent clearance (CL/F) were: weight, body surface area, sex, age, race, calculated creatinine clearance, serum creatinine, SGOT, SGPT, smoking status, and diabetes status. From these covariates, only SGOT was a significant predictor of eplerenone CL/F with a 27% decrease in CL/F for a doubling of SGOT. The model estimated apparent clearance for eplerenone as 4.91 L/hr with a 95% confidence interval of 3.81-6.81 L/hr.
A secondary analysis was performed to assess the patient covariates of weight, body surface area, sex, age, race on the apparent volume of distribution (V/F), and H2 antagonist usage and proton pump inhibitor usage on the relative bioavailability (Frel). Age, weight and sex were found to influence V/F. V/F was predicted to be nearly proportional to weight and nearly inversely proportional to age. The males were predicted to have a 28.3% decrease in V/F relative to females of similar age and weight.
The expressions for clearance and volume in the final model are shown below.

$$CL/F_g = \theta_3\left(\frac{SGOT}{25\,(\text{units/L})}\right)^{\theta_5}\exp\left(\eta_i^{CL} + \kappa_g^{CL}\right)$$

$$V/F = \theta_4\left(\frac{age}{65\,\text{yrs}}\right)^{\theta_7}\left(\frac{weight}{70\,\text{kg}}\right)^{\theta_8}\theta_9^{sex}$$

Results of final model parameter estimates and bootstrap results are shown in Table 1.

Table 1.

Conditional Final Model Parameter Estimates and Bootstrap Results

	Final Model	Bootstrap Results	
Parameter	Estimate ± SE	Estimate ± SE	95% CI
ka (1/hr)	1.61 ± 0.27	1.97 ± 0.51	1.11 - 3.14
CL/F (L/hr)	4.91 ± 0.35	5.15 ± 0.72	3.81 - 6.81
SGOT	-0.448 ± 0.111	-0.255 ± 0.190	-0.609 - 0.114
V/F (L)	39.7 ± 3.9	37.6 ± 4.53	32.0 - 51.4
Age	-0.804 ± 0.278	-0.790 ± 0.326	-1.49 - -0.161
Weight	0.798 ± 0.262	0.990 ± 0.391	0.398 - 1.99
Sex	0.717 ± 0.086	0.709 ± 0.100	0.514 - 0.906
σ (~%CV)	26.3 ± 3.1	25.8 ± 3.3	19.1 - 32.3

The analysis performed by the sponsor can be considered only as conditional because it was performed on the only part of the data with the small absorption time. The skewed WRES and Bayes predictions of the variance components indicates the population mean (typical value) fit to the data may not represent the best prediction of the data's central tendency (see Appendix). The skewed nature of the residuals is most likely due to a mixture of distributions that could not be partitioned by the extended least squares procedure for fitting the model and due to the amount of data at hand. Nevertheless, the one-compartment model predicts the plasma concentrations of the conditional data set well.

Were the eplerenone pharmacokinetic parameters estimated for CHF patients comparable with the other groups of patients?

The sponsor compared the estimated in Studies 058 and 035 pharmacokinetic parameters with the same parameters of eplerenone obtained in the previous studies (original NDA 21-437). The bootstrap 95% confidence interval for clearance (Table 1) also contains the mean estimate reported for the elderly in an elderly versus young pharmacokinetic study, NE3-01-06-028 and overlaps the 95% confidence interval of the Black/Caucasian population. The between-patient coefficient of variation (CV) for CL/F was estimated to be negligible, while the within-patient (inter-occasion) CV was estimated as 63.2%, an estimate similar to that of the Black/Caucasian hypertension population (57.3%).
The plasma concentrations were higher in the CHF patients than in the hypertensive patients, which is consistent with the CHF patients' lower estimate of apparent clearance. The reduction in CL/F observed in CHF patients may be due to the older age distribution of these patients (median age of 64) relative to the age distribution of the healthy volunteer studies, EE3-96- 02-001, EE3-96-02-004, and EE3-96-02-005, and the age distribution of hypertensive patients. In the young versus elderly healthy volunteer study (NE3-01-06-028), the elderly patients' estimate (N=24) of CL/F was reported to be 6.60 L/hr versus 9.63 L/hr in the young, (N=23), a number in between the CHF population estimate (4.91 L/hr) and the hypertensive estimate (7.33 L/hr). The age distribution for the CHF patients is larger than the hypertensive patients of IE3-01-08-020 (median age of 52.5). Additionally, the clearance estimate of 4.91 L/hr (95% CI: 3.81-6.81 L/hr) in the EPHESUS sub-study was comparable to the mean apparent clearance of 5.36 L/hr

(geometric mean, determined at steady-state after 5 days of dosing) reported in a prospective pharmacokinetic study of eplerenone in CHF patients (058).

Is there a dose dependent effect on hormones?

Hormones were not measured in the trials submitted on April 4, 2003. This submission included

- study 058 a study that examined the effect of chronic CHF on eplerenone pharmaockinetics,
- study 011, a phase 2 heart failure study,
- study 402, a dose ranging study in symptomatic heart failure, and
- study 035, a phase 3 post-MI heart failure study (EPHESUS).

A pharmacokinetic study, EE3-96-02-004, submitted on November 28, 2001 (serial number 000) contained hormone and drug concentration data. This was a double-blind, randomized, placebo-controlled, rising oral dose study in 40 healthy males. Patients were dosed eplerenone 100 mg, 300 mg, 1000 mg, spironolactone 100 mg or placebo daily for eleven days. The following hormones were measured: dihydrotestosterone, estradiol, free testosterone, total testosterone, luteinizing hormone, follicule stimulating hormone, free thyroxine and thyroid stimulating hormone. Hormone levels were measured around trough or 12 hours after the dose at baseline (Day 1) and on Days 3, 7 and 11. Nonlinear mixed effects modeling did not show any significant effects of dose on hormone concentration.

5 LABELING COMMENTS

GENERAL

1. The Agency considered that the information provided in the Supplement No. SE1 002 to NDA 21,437 for Inspra tablets was appropriate to evaluate the pharmacokinetic of eplerenone in heart failure patients.

CLINICAL PHARMACOLOGY COMMENTS

2. The pharmacokinetics of eplerenone and its metabolites were compared in CHF patients and matched control subjects in the prospective Study 058. The plasma levels of eplerenone, SC-70303 (open-ring form of eplerenone) and SC-71597 (primary inactive metabolite) in CHF patients were higher than in the matched control group. However, all differences in the pharmacokinetic parameters (AUC and Cmax) in the CHF patients and the matched control subjects were statistically insignificant. This may be in part due to a very high inter-subject variability and insufficient sample power. Nevertheless, these differences were not considered as clinically important.
3. The sponsor analyzed the sparse sampling data obtained from the sub-study of EPHESUS (035) using a population PK approach. The sponsor's one-compartmental model estimated the apparent clearance as 4.9 L/kg. This value is about twice lower than the clearance values estimated for the group hypertensive patients and similar with the clearance values for the healthy elderly subjects.
4. Given the large within-patient variability in CL/F, dose adjustments for CHF patients are not warranted.

Labeling Comments:

1. CLINICAL PHARMACOLOGY Section,
Special Population, Heart Failure. The suggested labeling is as follows:

Heart Failure: [

]

Dosing Recommendations:

The sponsor recommended dose of INSPRA is 50 mg once daily. Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably

within 4 weeks as tolerated by the patient. INSPRA may be administered with or without food. Since the pharmacokinetic differences between HF patients and healthy matched control group were not statistically and clinically significant, the dose recommendation deemed appropriate. The language in this section proposed by the sponsor is acceptable.

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6 APPENDIX

6.1 Review of Individual Studies

6.1.1 Effect of Chronic Congestive Heart Failure on the Pharmacokinetic of Eplerenone" (report NE3-01-02-058)

Study Period:
June 2002-August 2002.

Investigator and Center:
[redacted]

Objectives:
Primary Objective: To determine the effect of chronic congestive heart failure (CHF) on the single dose and multiple dose pharmacokinetics of eplerenone (50 mg).
Secondary Objective: To determine the safety and tolerability of eplerenone (50 mg) in subjects diagnosed with chronic CHF.
Design:
This pharmacokinetic study utilized a two-period, open-label, single-dose and multiple dose design in 16 subjects; 8 subjects diagnosed with CHF and 8 matched-control subjects. Each control subject was matched to a CHF subject by sex, age (10 years) and weight (30%). Serial plasma and urine samples were collected on Days 1 and 7.

Potassium and magnesium measurements were collected on Days 1, and Days 4, 5 and 7 at predose and 6 hours postdose. Vital signs were measured once daily, but more frequently on Day 1 and Days 3-7 at the following timepoints: 15 minutes predose and 1.25, 2.5 and 7 hours postdose.

All enrolled subjects were included in safety analyses using two datasets: 1) all enrolled subjects and 2) excluding one CHF subject with unusually high eplerenone plasma concentrations. All enrolled subjects were included in the safety analyses.

Treatments Administered:
Subjects received a single 50 mg eplerenone dose on Day 1, followed by once-daily 50 mg doses of eplerenone on Days 3-7.

Table 1. Identity of Test Product

Drug	Strength	Route	Potency	Pkg Lot	Mfg Lot	Mfg Date	Exp Date
Eplerenone	50 mg	Oral	99.6%	RCT 11872	PT- 069- 99	6/99	6/04

All investigational drug supplies were stored in a secured and temperature-controlled area that had restricted access. The clinical site was responsible for study drug administration and inventory.

Biologic Samples:
Plasma samples for pharmacokinetic analyses for eplerenone (SC-66110), the inactive, open-ring form of eplerenone (SC-70303) and the inactive, primary metabolite (SC-71597) were collected on Days 1 and 7 at the following time points: 10 minutes prior to study drug dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours postdose; additional samples were collected at 36 and 48 hours postdose on Day 1. Plasma samples were collected on Days 4-6 at 10 minutes predose. Urine samples were collected and pooled from 10 hours immediately prior to dosing, and between 0-24 and 24-48 hours postdose on Day 1 and between 0-24 hours postdose on Day 7.

Bioanalytical Method:
Samples were analyzed for eplerenone, SC-70303 and SC-71597 in plasma by and in urine by using . Lower limits of quantification (LLOQ) for each analyte are shown in Table 2.

Table 2. Lower Limit of Quantitation for Eplerenone Assays

Analyte	Plasma	Urine
Eplerenone	ng/mL	ng/mL
SC-70303	ng/mL	ng/mL
SC-71597	ng/mL	ng/mL

Endpoints:
The primary pharmacokinetic endpoints were eplerenone AUCs, Cmax, Tmax, Vss/F, T1/2, MRT, XU0-t (where t=24 hr and 48 hr) and CL/F. Secondary pharmacokinetic endpoints included Cmax and AUC values for SC-70303 and SC-71597.

The secondary endpoints were laboratory safety test results, 12-lead ECGs, neurohormonal and peptide levels, physicals, vital signs (heart and respiration rates, blood pressure, and temperature), and type and frequency of adverse events.

Statistical Methods:

An analysis of covariance (ANCOVA) was performed on eplerenone, SC-70303 and SC-71597 AUCs, Cmax, Tmax, Vss/F and XUs, for each day separately. Prior to the ANCOVA, AUCs, Cmax, Vss/F and XUs were natural log-transformed. The sources of variation included in the ANCOVA model were subject group and body weight as covariate.

The subjects with heart failure and matched controls were compared within the ANCOVA as follows: estimate statements were used to obtain estimates of the least squares mean difference between the subjects with heart failure and matched-control subjects. Ninety (90%) confidence intervals were constructed for the mean differences. The point estimates of the mean differences and the endpoints of the 90% confidence intervals on the logarithmic scale were exponentiated to obtain the ratios of the geometric least squares means and the corresponding 90% confidence intervals on the original scale. The p-value for the group comparison was calculated from the ANCOVA model.

Morning predose plasma concentrations of eplerenone, SC-70303 and SC-71597 from Days 3-7 were analyzed using repeated measures analysis of variance to assess whether steady-state conditions had been reached by Day 5.

Results:

Demographic and baseline characteristics are shown in Table 3.
Table 3. Demographic and Baseline Characteristics

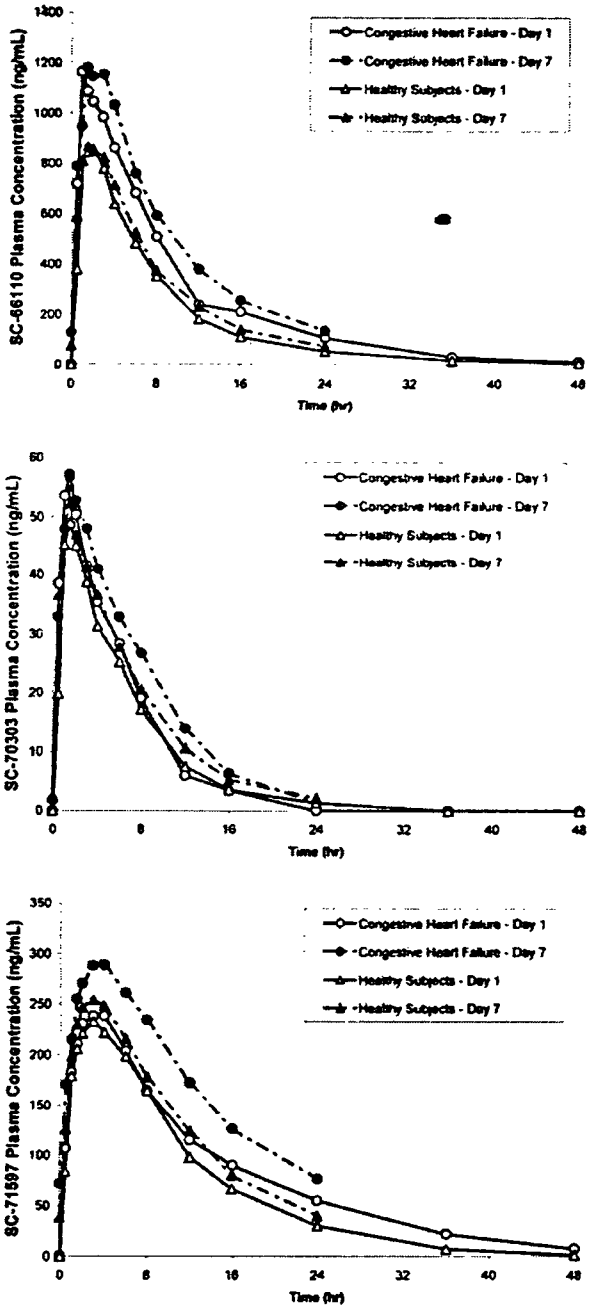
	Subjects with Congestive Heart Failure N= 8	Matched Controls N = 8
Age (yr)		
Mean (SD)	55.6 (15.87)	54.4 (14.70)
Range	33 – 80	40 – 78
Ethnicity (N, %)		
White	6 (75.0%)	8 (100.0%)
Black	2 (25.0%)	0 (0%)
Sex (N, %)		
Female	3 (37.5%)	3 (37.5%)
Male	5 (62.5%)	5 (62.5%)
Weight (kg) [Mean (SD)]		
Female	63.93 (17.702)	76.37 (19.116)
Male	107.5 (28.843)	95.38 (15.296)
Height (cm) [Mean (SD)]		
Female	158.77 (6.350)	161.70 (1.473)
Male	180.82 (7.784)	178.54 (9.398)

Subjects ranged in age from 33 to 80 years, with mean ages of 55.6 years for CHF subjects and 54.4 for matched-control subjects. In both subject groups, the majority of subjects were white (75%) and male (62.5%).

Pharmacokinetic Results:

As shown in Figure 1, mean plasma concentrations of eplerenone among subjects with CHF were slightly greater than those among control subjects following both single and multiple doses of eplerenone. Mean plasma concentrations of SC-70303 were similar between the two subjects groups following both single and multiple doses of eplerenone. Compared to matched controls, subjects with CHF had similar mean plasma concentrations of SC-71597 following a single dose of eplerenone, but greater plasma concentrations following multiple doses of eplerenone.

Figure 1. Mean Eplerenone, SC-70303 and SC-71597 Plasma Concentrations after Single- and Multiple-Dose Administration (Including Subject 0102)



The results of the repeated measures analysis on trough plasma concentrations of eplerenone on Days 3-6 indicate that steady-state concentration was achieved after two days of dosing in both subject groups (day effect p-values were ≥ 0.1218).

Using data from all randomized subjects, there were no statistically significant differences between CHF subjects and control subjects regarding any of the calculated eplerenone, SC-70303 or SC-71597 pharmacokinetic parameters following either single or multiple dosing. Overall, eplerenone, SC-70303 and SC-71597 AUCs and Cmax values increased 37.7% for eplerenone, 34.6% for SC-70303 and 29.5% for SC-71597. All differences in CHF subjects compared to the matched controls were statistically insignificant. None of these increases were considered clinically important. The mean (CV, %) pharmacokinetic parameters calculated on Day 1 and Day 7 are listed in Table 4.

Table 4. Arithmetic Mean Eplerenone Plasma Pharmacokinetic Parameters (Including Subject 0102)

	Day 1		Day 7	
	Subjects with Congestive Heart Failure N= 8	Matched-Control Subjects N = 8	Subjects with Congestive Heart Failure N= 8	Matched-Control Subjects N = 8
Eplerenone				
AUC (hr*ng/mL) (a)	11070.6 (80.5%)	7737.3 (49.1%)	11622.0 (85.2%)	7892.8 (56.7%)
Cmax (ng/mL)	1170.4 (48.4%)	1026.6 (16.2%)	1418.0 (55.3%)	1023.6 (26.0%)
Tmax (hr)	1.6 (27.1%)	1.6 (46.8%)	1 6 (49.7%)	1.8 (37.4%)
T1/2 (hr)	6.2 (45.4%)	5.2 (62.2%)	NAP	NAP
CL/F (L/hr)	6.3 (50.4%)	8.5 (67.5%)	6.1 (51.1%)	9.3 (88.0%)
CL/F/WT (L/hr70kg)	6.0 (87.1%)	7.9 (100.2%)	6.0 (88.9%)	9.0 (122.9%)
Vss/F (L)	48.9 (38.8%)	48.8 (23.9%)	37.0 (34.0%)	44.5 (28.5%)
XU (µg) (b)	1330.0 (60.2%)	1435.1 (69.7%)	1208.3 (36.4%)	1569.9 (118.8%)
SC-70303				
AUC (hr*ng/mL) (a)	504.4 (40.2%)	393.7 (55.4%)	427.1 (45.9%)	371.8 (70.3%)
Cmax (ng/mL)	64.9 (63.7%)	56.1 (37.9%)	66.8 (39.5%)	59.0 (33.2%)
Tmax (hr)	1.6 (42.3%)	1.5 (50.4%)	1.7 (41.6%)	1.6 (48.7%)
T1/2 (hr)	6.7 (58.9%)	5.0 (55.4%)	NAP	NAP
XU (µg) (b)	3436.8 (42.7%)	3106.1 (63.2%)	3455.2 (45.7%)	3236.6 (92.1%)
SC-71597				
AUC (hr*ng/mL) (a)	3896.5 (34.4%)	3115.3 (31.0%)	4178.5 (34.6%)	3194.7 (35.8%)
Cmax (ng/mL)	267.5 (41.4%)	252.9 (32.8%)	327.3 (34.8%)	290.5 (32.5%)
Tmax (hr)	3.5 (61.0%)	3.1 (56.9%)	3.1 (55.8%)	3.2 (48.9%)
T1/2 (hr)	8.4 (43.2%)	6.8 (46.1%)	NAP	NAP
XU (µg) (b)	8706.3 (44.8%)	9824.3 (24.5%)	8336.2 (37.2%)	8950.8 (17.0%)

(a) AUC(0-∞) for Day 1 and AUC(0-24) for Day 7.
(b) XU(0-48) for Day 1 and XU(0-24) for Day 7.
NAP = Not Applicable.

For one subject (#0102, 42-years old African-American female) eplerenone plasma concentrations were elevated almost 2-fold greater than for the other CHF subjects. When the sponsor analyzed the specifics of disease state and administered co-medications, the sponsor concluded that none of those might affect the pharmacokinetic of eplerenone. To evaluate the outlier nature of the data from subject 0102, statistical analyses were performed including and excluding Subject 0102. Without the data from subject 0102, the eplerenone, SC-70303 and SC-71597 mean plasma exposures (AUCs) and peak plasma concentrations (Cmax) increased in CHF subjects compared to matched controls by 15.1% for eplerenone, 30.3% for SC-70303 and 23.8% for SC-71597. These differences were statistically insignificant. None of these changes were considered clinically meaningful.

Table 5 lists the ratios and 90% CIs for eplerenone and its metabolites (including subject 0102).

Table 5.

Ratios, 90% Confidence Intervals, and Corresponding P-Values for Eplerenone Pharmacokinetic Parameters (Including Subject 0102)

Pharmacokinetic Parameter	Least Squares Means (a)		Ratio CHF/Control	90% CI for Ratio	P-Value (b)
	CHF N = 8	Control N = 8			
Eplerenone					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	8737.64	6796.36	1.286	(0.750, 2.203)	0.423
AUC(0-∞) (hr*ng/mL)	8957.38	6961.13	1.287	(0.747, 2.217)	0.427
Cmax (ng/mL)	1080.86	1011.14	1.069	(0.796, 1.436)	0.696
CL/F (L/hr)	5.58	7.18	0.777	(0.451, 1.339)	0.427
CL/F/WT (L/hr/70 kg)	4.60	5.74	0.802	(0.393, 1.634)	0.592
Vss/F (L)	45.45	46.85	0.970	(0.683, 1.378)	0.881
XU (µg) (c)	1085.56	1172.21	0.926	(0.476, 1.803)	0.841
Tmax (hr)	1.61	1.58	--	--	0.934
T1/2 (hr)	6.22	5.23	--	--	0.545
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	9331.42	6776.82	1.377	(0.754, 2.513)	0.364
Cmax (ng/mL)	1277.44	984.86	1.297	(0.900, 1.869)	0.230
CL/F (L/hr)	5.36	7.38	0.726	(0.398, 1.325)	0.364
CL/F/WT (L/hr/70 kg)	4.53	5.90	0.767	(0.352, 1.672)	0.558
Vss/F (L)	34.62	42.80	0.809	(0.572, 1.144)	0.298
XU (µg) (c)	1157.52	1085.85	1.066	(0.610, 1.864)	0.843
Tmax (hr)	1.55	1.76	--	--	0.591
SC-70303					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	285.24	265.11	1.076	(0.641, 1.805)	0.806
AUC(0-∞) (hr*ng/mL)	469.92	349.23	1.346	(0.877, 2.065)	0.241
Cmax (ng/mL)	56.67	51.31	1.104	(0.724, 1.685)	0.684
XU (µg) (c)	3151.49	2622.39	1.202	(0.717, 2.015)	0.540
Tmax (hr)	1.60	1.53	--	--	0.842
T1/2 (hr)	6.65	5.10	--	--	0.399
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	395.09	302.11	1.308	(0.782, 2.186)	0.372
Cmax (ng/mL)	63.59	54.92	1.158	(0.844, 1.589)	0.427
XU (µg) (c)	3278.75	2510.34	1.306	(0.793, 2.152)	0.361
Tmax (hr)	1.68	1.63	--	--	0.905
SC-71597					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	3426.01	2821.65	1.214	(0.910, 1.620)	0.254
AUC(0-∞) (hr*ng/mL)	3710.61	2990.00	1.241	(0.922, 1.670)	0.220
Cmax (ng/mL)	247.44	234.25	1.056	(0.696, 1.599)	0.819
XU (µg) (c)	7949.95	9502.20	0.837	(0.584, 1.198)	0.395
Tmax (hr)	3.49	3.07	--	--	0.689
T1/2 (hr)	8.40	6.79	--	--	0.385
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/Ml)	3927.09	3032.24	1.295	(0.919, 1.825)	0.204
Cmax (ng/mL)	310.24	271.79	1.141	(0.792, 1.646)	0.533
XU (µg) (c)	7934.05	8694.92	0.912	(0.696, 1.197)	0.560
Tmax (hr)	3.16	3.15	--	--	0.992

(a) Based on ANCOVA model with subject group as factor and body weight as the covariate. A natural log transformation for AUC, Cmax and XU parameters was used prior to the ANCOVA.
(b) P-value from the ANCOVA model for the subject group comparison.
(c) XU(0-48) for Day 1 and XU(0-24) for Day 7.
Source: Tables T9.1.1, T9.1.2, T9.2.1, T9.2.2, T9.3.1, and T9.3.2

Table 6 lists the same parameters calculated without subject 0102.

Table 6. Ratios and 90% Confidence Intervals for Eplerenone, SC-70303 and SC-71597 Pharmacokinetic Parameters (Excluding Subject 0102)

Pharmacokinetic Parameter	Least Squares Means (a)		Ratio CHF/Control	90% CI for Ratio	P-Value (b)
	CHF N = 7	Control N = 8			
Eplerenone					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	7307.25	6769.82	1.079	(0.684, 1.704)	0.771
AUC(0-∞) (hr*ng/mL)	7500.86	6934.80	1.082	(0.679, 1.724)	0.769
Cmax (ng/mL)	963.26	1010.14	0.954	(0.769, 1.182)	0.700
CL/F (L/hr)	6.67	7.21	0.925	(0.580, 1.473)	0.769
CL/F/WT (L/hr/70 kg)	5.46	5.77	0.946	(0.474, 1.886)	0.887
Vss/F (L)	52.05	47.00	1.107	(0.852, 1.440)	0.502
XU (µg) (c)	1251.28	1175.36	1.065	(0.550, 2.061)	0.869
Tmax (hr)	1.56	1.58	--	--	0.952
T1/2 (hr)	6.03	5.23	--	--	0.648
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	7746.22	6754.75	1.147	(0.675, 1.947)	0.653
Cmax (ng/mL)	1132.54	983.92	1.151	(0.846, 1.567)	0.432
CL/F (L/hr)	6.45	7.40	0.872	(0.514, 1.481)	0.653
CL/F/WT (L/hr/70 kg)	5.43	5.93	0.917	(0.430, 1.956)	0.842
Vss/F (L)	39.90	42.90	0.930	(0.733, 1.181)	0.599
XU (µg) (c)	1155.71	1088.20	1.062	(0.580, 1.943)	0.862
Tmax (hr)	1.35	1.76	--	--	0.245
SC-70303					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	306.11	265.75	1.152	(0.670, 1.980)	0.650
AUC(0-∞) (hr*ng/mL)	439.68	349.10	1.259	(0.809, 1.960)	0.371
Cmax (ng/mL)	60.52	51.56	1.174	(0.757, 1.821)	0.528
XU (µg) (c)	3447.96	2620.20	1.316	(0.777, 2.228)	0.371
Tmax (hr)	1.55	1.52	--	--	0.941
T1/2 (hr)	5.55	5.07	--	--	0.748
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	394.46	302.69	1.303	(0.748, 2.271)	0.412
Cmax (ng/mL)	66.55	55.13	1.207	(0.867, 1.681)	0.331
XU (µg) (c)	2924.81	2510.24	1.165	(0.717, 1.894)	0.585
Tmax (hr)	1.50	1.63	--	--	0.722
SC-71597					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	3308.09	2819.87	1.173	(0.866, 1.589)	0.367
AUC(0-∞) (hr*ng/mL)	3606.73	2989.06	1.207	(0.880, 1.654)	0.310
Cmax (ng/mL)	239.40	234.42	1.021	(0.656, 1.591)	0.934
XU (µg) (c)	8888.66	9522.84	0.933	(0.681, 1.280)	0.704
Tmax (hr)	3.42	3.07	--	--	0.754
T1/2 (hr)	8.43	6.79	--	--	0.410
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/Ml)	3750.91	3028.99	1.238	(0.865, 1.773)	0.309
Cmax (ng/mL)	304.55	271.90	1.120	(0.758, 1.660)	0.617
XU (µg) (c)	7848.02	8710.77	0.901	(0.673, 1.206)	0.536
Tmax (hr)	2.75	3.15	--	--	0.629

(a) Based on ANCOVA model with subject group as factor and body weight as the covariate. A natural log transformation for AUC, Cmax and XU parameters was used prior to the ANCOVA.
(b) P-value from the ANCOVA model for the subject group comparison.
(c) XU(0-48) for Day 1 and XU(0-24) for Day 7.

Comments:

1. The variabilities of the plasma concentrations (CV) over the first 12 hours post-dose were 26-88% for eplerenone, 13-119% for SC-70303 and 29-140% for SC-71597. The variabilities of the trough plasma concentrations (CV) were 100-280% for eplerenone, 280% for SC-70303 and 65-280% for SC-71597. When pharmacokinetic parameters were compared between subjects with CHF and matched control subjects following single or multiple doses of eplerenone, the increase in eplerenone AUC was about 38% and Cmax about 30%, resulting in CL/F decrease of about 27%. However, these differences were found to be statistically insignificant probably due to the high variability in data.
2. The sponsor concluded that compared to healthy subjects, CHF subjects showed no clinically important increase in total plasma exposure (AUC) to eplerenone. The Agency decided for the other special populations that these differences are not clinically significant.
3. The results of this study bridge the pharmacokinetics of eplerenone in congestive heart failure patients with those in healthy volunteers.

6.2.1 Eplerenone Population Pharmacokinetic Modeling in Post-AMI Patients with Left Ventricular Dysfunction and Clinical Symptoms of Heart Failure Substudy: A Substudy of Study IE3- 99- 02- 035

Objectives:
The primary objective of this substudy was to summarize the pharmacokinetics of eplerenone in the left ventricular dysfunction/heart failure population and to determine patient covariates that affect the key pharmacokinetic parameter, apparent clearance (CL/F).
The secondary objective was to determine covariates that influence other pharmacokinetic parameters (absorption, apparent volume of distribution, etc.). A pharmacokinetic analysis plan was prepared to address many of the data analysis issues (such as defining the covariates) a priori.

Study Design:

A pseudo-random design was used for eplerenone (SC-66110) plasma concentration samples. Patients participating in the population pharmacokinetic sub-study had a blood sample drawn prior to and 1-hour after the administration of the first dose of active study medication (Day 0). At week 1 (Visit 2) and at 6 months (Visit 5) patients had two blood samples collected approximately one hour apart. The sample time, defined as the time relative to the last dose, was calculated by subtracting the patient's last recalled dose time from the blood collection time. The sampling design was considered pseudo-random since no restrictions were placed on the duration of time between the most recent dose and the time of the first blood sample. However, investigators were instructed to schedule one morning visit and one afternoon visit to ensure a wide distribution of sample times. Month 6 had a higher frequency of later sample times indicating increased afternoon sampling.

Covariate Data
Descriptive statistics for the patients' covariates considered in building the population pharmacokinetic model are displayed in Table 1 and Table 2 for the continuous and discrete covariates, respectively. The symbols used in Table 2 are defined as follows: Sex, F=female and M=male; Race, A=Asian, B=Black, C=Caucasian, H=Hispanic, and O=Other; Smoking Status, C=current, F=former, and N=never; Diabetes, N=no and Y=yes; and for the concomitant medication usage N=no and Y=yes. Covariate imputations and repeat labs were minor. For patient 6008 repeat lab values were used for Day 0/Week 1 (Scre, SGOT, SGPT). Weight was imputed for Week 1 using Day 0 for patients 6192, 6757, 6975, 7189, 7457, 7528, 7650, and 7655, and was imputed using the closest measurement for patient 4760. Diabetes status is defined in Table 2 as a baseline covariate. The time of meal relative to dose was not collected from the patients. Therefore, it was not considered in the population pharmacokinetic model.

Table 1. Descriptive Statistics for the Continuous Covariates

Covariate		Baseline (N=113)*		
Age (yrs)	Mean ± SD	63.6 ± 10.2		
	Median	64.0		
	Min-Max	42-83		
		Time Dependent		
		Day 0 (N=89)	Week 1 (N=65)	Month 6 (N=59)
Weight (kg)	Mean ± SD	77.7 ± 14.4	77.6 ± 12.6	77.6 ± 13.8
	Median	77.0	77.0	76.3
	Min-Max	49-112	55.3-109	48 – 110.5
BSA (m^2)	Mean ± SD	1.87 ± 0.19	1.87 ± 0.17	1.86 ± 0.19
	Median	1.88	1.86	1.85
	Min-Max	1.49-2.36	1.56-2.30	1.48-2.27
Scre (mg/dL)	Mean ± SD	1.18 ± 0.30	1.17 ± 0.28	1.15 ± 0.37
	Median	1.17	1.17	1.10
	Min-Max			
CrCl (mL/min)	Mean ± SD	71.8 ± 25.8	72.1 ± 25.4	75.1 ± 28.6
	Median	69.7	68.5	76.8
	Min-Max			
SGOT (unit/L)	Mean ± SD	35.5 ± 20.2	35.2 ± 21.1	21.8 ± 9.0
	Median	29	28	20
	Min-Max			
SGPT (unit/L)	Mean ± SD	47.5 ± 40.6	46.2 ± 41.3	22.0 ± 13.2
	Median	34	32	19
	Min-Max			

Table 2. Descriptive Statistics for the Discrete Covariates

Covariate		Baseline (N=113)*		
Sex	No.	33 F / 80 M		
	(%)	29.2 / 70.8		
Race	No.	14 A / 93 C / 0 B / 2 H / 4 O		
	(%)	12.4 / 82.3 / 0.0 / 1.8 / 3.8		
Smoking Status	No.	36 C / 31 F / 46 N		
	(%)	31.9 / 27.4 / 40.7		
Diabetes	No.	79 N / 34 Y		
	(%)	69.9 / 30.1		
		Time Dependent		
		Day 0 (N=89)	Week 1 (N=65)	Month 6 (N=59)
Estrogen Therapy	No.	88 N / 1 Y	65 N	58 N / 1 Y
	(%)	98.9 / 1.1	100.0	98.3 / 1.7
Thyroid Therapy	No.	89 N	64 N / 1 Y	59 N
	(%)	100.0	98.5 / 1.5	100.0
H2 Antagonist Usage	No.	85 N / 4 Y	60 N / 5 Y	54 N / 5 Y
	(%)	95.5 / 4.5	92.3 / 7.7	91.5 / 8.5
Proton Pump Inhibitor Usage	No.	88 N / 1 Y	65 N	58 N / 1 Y
	(%)	98.9 / 1.1	100.0	98.3 / 1.7

The sponsor commented that inspection of these tables reveals that the marginal distribution of CrCl, SGOT, and SGPT changed from Day0/Week1 to Month 6. CrCl increased approximately 17%, while SGOT and SGPT decreased approximately 31% and

44%, respectively. To assess whether this marginal change reflected a real intrapatient change, percent change between Day0/Week1 and Month 6 was calculated for each patient.
The sub-population selected for the PK study
(12.4 Asian/ 82.3 Caucasian/ 0 Black/ 1.8 Hispanic/ 3.8 Other %) had much higher 12.4% versus 0.97% of Asian patients involved. Therefore, it is possible that the conclusions regarding the influence of SGOT on the apparent clearance values drawn for the post MI patients may be improper.

Data:
The sponsor deleted some data due to missing concentrations, data errors and other issues discovered during the model development. Out of 726 samples, 34 data values had missing or inaccurate dose time; 11 data values had missing concentration value; 186 samples were assayed below the detection limit. The sponsor discovered that the lag-time values for drug absorption had a mixture distribution. Only the patients with small lag-time were chosen for the final model run. Thus 7 patients and 82 plasma concentrations were excluded due to the excessively long lag-times. The final population model was supported by 113 patients (84.3%) with 324 plasma concentrations (44.6%) out of the original 134 patients and 726 plasma concentrations.

Model Development
Base Model
A one-compartment model, implemented in the PREDPP subroutine ADVAN2 of the NONMEM software, was used to describe the eplerenone concentration-time profiles. The structural model was parameterized in terms of an absorption lag-time (Tlag), an absorption rate constant (ka), the apparent volume of distribution (V/F), and the apparent clearance (CL/F).
The pharmacokinetic parameter sub-models included random effects for inter-patient (IIV) and inter-occasion variability (IOV). The sub-models were expressed as [1]:

$$\theta_{ij} = \theta_0 \exp(\eta_i + \kappa_{ij}),$$

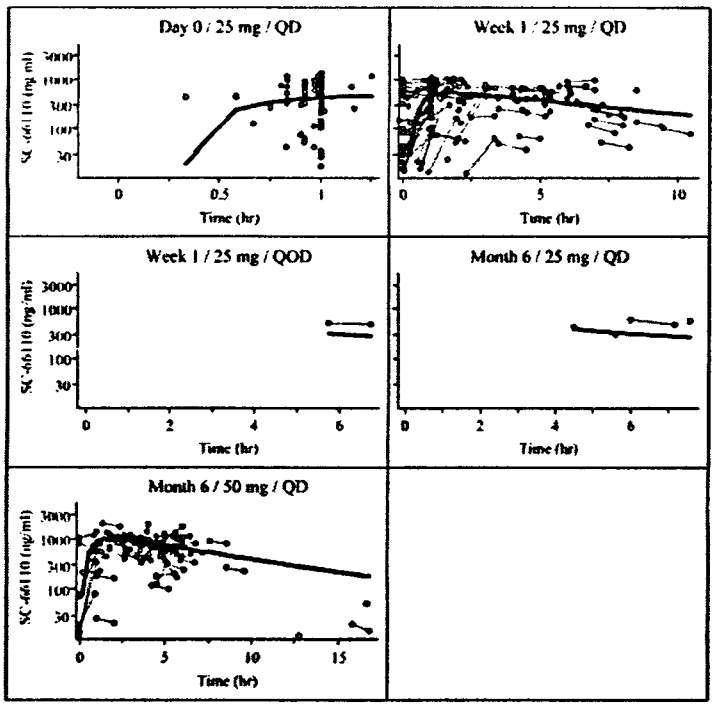
where θ_{ij} represents the value of the pharmacokinetic parameter (e.g. CL/F) for patient *i* for period (occasion) j, θ_0 represents the population mean (typical value), η_j denotes a random deviation from θ_0 for patient i, and κ_{ij} denotes the random deviation from individual i's prediction for occasion *j* (Day 0, Week 1, or Month 6). The η_j's and κ_{ij}'s are assumed to have zero means and covariance matrices, Ω_{IIV} and Ω_{IOV}. The square roots of the diagonal elements of Ω_{IIV} and Ω_{IOV} are interpreted as approximate coefficients of variation (CVs).
The natural logarithm was assumed to stabilize the intrasubject variability in the pharmacokinetic data. The 'transform both sides approach' yielded the model [2]

$$\ln(oc_{ijk}) = \ln(c(t)_{ijk}) + \varepsilon_{ijk},$$

where oc_{ijk} denotes the observed eplerenone plasma concentration for subject i at visit j for measurement t_k, $c(t)_{ijk}$ denotes the expected value of the concentration under the model, and ε_{ijk} denotes the intrasubject random (residual) error. The ε_{ijk} are assumed to be independent, have zero mean, and variance, σ^2, where σ is the approximate CV. The population model using Eqns. [1] and [2] is hereafter referred to as the "base model", since no covariates are included in the sub-models for the pharmacokinetic parameters. The first-order conditional estimation (FOCE) method was used to estimate the parameters and variance components and provide the Bayes predictions of the η_j's and κ_{ij}'s.

The sponsor evaluated the fit of the one-compartment model described to the pharmacokinetic data excluding the missing concentrations and inaccurate dose-time data. The residual distribution was highly skewed and bimodal. The residual variability showed a CV of 43.2% (Figure 1).

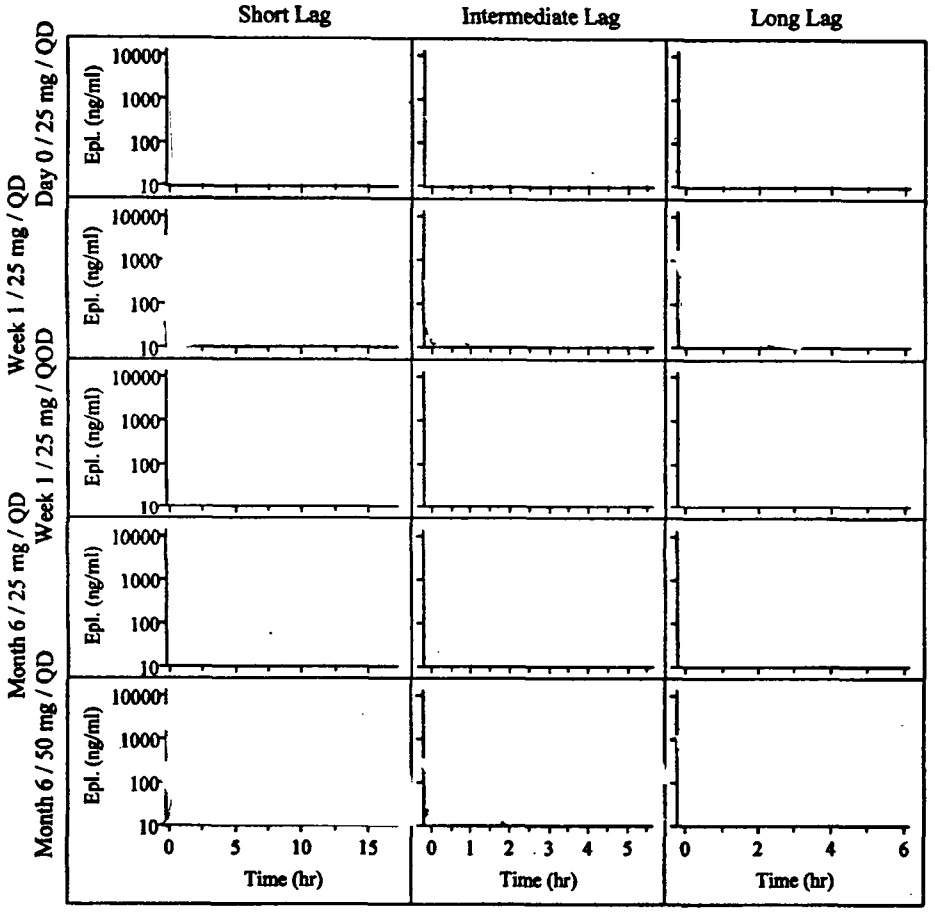
Figure 1. Base Model Fit with Aberrant Absorption Lag-times and Observed Eplerenone Plasma Concentrations and Base Model Fit



The sponsor mentioned that the data from the 7 patients contained a rapid rise in concentrations between the first and second sample time on at least one occasion. The sponsor used a mixture model to identify the lag-time distributions. For that, the between-patient variability was assumed negligible and each patient in the data file was given a new NONMEM ID variable value for each visit. A short, an intermediate, and a long lag-time distribution characterized the absorption lag-times. The final mixture model converged using the first-order estimation (FO) estimation method of NONMEM. The

mixture model predicted the constituents of the lag-time distributions (Figure 2).

Figure 2. Mixture Model Results – Partitioning the Data by Absorption Lag-times



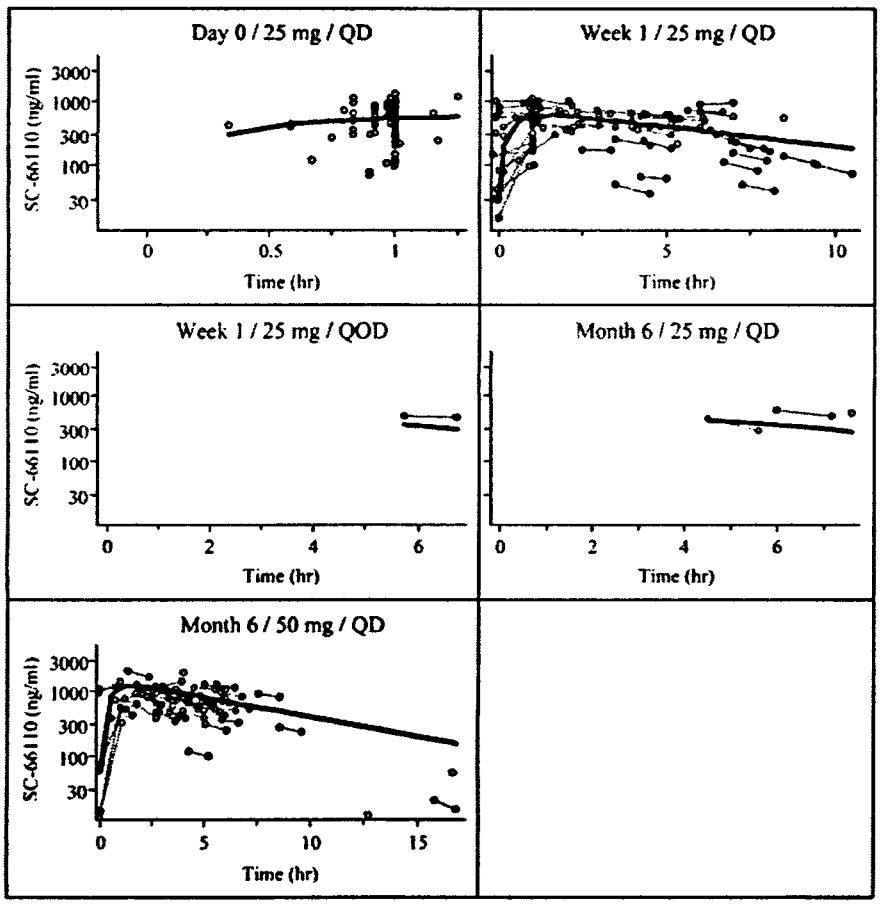
The short lag-time distribution (about 16 min) was estimated previously for the healthy volunteer data. The other two population's lag-time estimates were much greater, and were not observed in the healthy volunteer studies. The data with intermediate and long lag-times were dropped from the analysis. Since the final analysis was performed only using the data with short lag-time distribution, which represented only part of the patient population, the sponsor considered this data analysis as conditional.

Results

A total of 258 patients with 1416 plasma concentrations were enrolled in the population pharmacokinetic sub-study, but only 134 eplerenone patients with 726 samples were analyzed. An initial attempt to fit a full, unstructured covariance matrix for the IIV (interindividual or between-patient) and IOV (interoccasion or within-patient) was unsuccessful. This model had difficulty converging and suffered rounding errors due to

over-parameterization. The model assuming an IIV variance component only on ka and IOV variance components only on CL/F was stable and parsimonious. Tlag could no be estimated (the Hessian matrix was non- positive definite) and the sponsor used Tlag=0 fixed. The base model was fit to obtain the population mean predictions shown in Figure 3.

Figure 3. Short Lag-time Eplerenone Concentrations and the Conditional Base Model Prediction



Although alll diagnostic plots were improved in comparison with the base model, the empirical Bayes predictions for ka and the WRES remained skewed, indicating that the population mean value might not represent the best prediction of the data's central tendency. Fitting mixture models was attempted, but these models were not pursued due to model instability in estimating the absorption rate.

Covariate Analysis

For the absorption parameters, Tlag and ka, covariates were not tested.
Based on the analysis of the plots of CL/F versus the covariates, possible correlations were revealed between CL/F and SGOT, SGPT, and smoking status. Table 3 below

displays the results of the stepwise procedure. SGOT and Diabetes status were added during the forward selection (the covariates showed a change in ELS > 5.03). However, backward elimination removed Diabetes status since it failed to maintain the 7.88 cutoff for model.

Table 3. Results of the primary stepwise model building procedure (CL/F)

Step[a]	Covariate	ELS	ΔELS (p-value)
0	Base Model	-62.744	--
1	SGOT – CL/F	-77.128	14.384 (<0.0002)
2	Diabetes – CL/F	-83.124	5.996 (0.0143)
-1	Diabetes – CL/F	-77.128	5.996 (0.0143)
Final	SGOT – CL/F	-77.128	14.384 (<0.0002)

[a]For each step, 1-2, the covariate parameter with the greatest ΔELS≥χ^2(1,0.025)=5.03 was reported and included in the model in the next step. For step –1, the covariate parameter with the smallest ΔELS≤ χ^2(1,0.005)=7.88 was eliminated. The covariates in the final step were included in the final model since their ΔELS>7.88.

In a secondary analysis, the covariates that could potentially influence V/F and the relative bioavailability fraction (Frel) were also tested using the stepwise procedures used above. H2 antagonist usage and proton pump inhibitor usage were pooled due to the similarity of indication and their minimal representation in this PK population. Results of the stepwise procedures revealed that age, weight, and sex influenced V/F. The results of the stepwise procedure are displayed in Table 4.

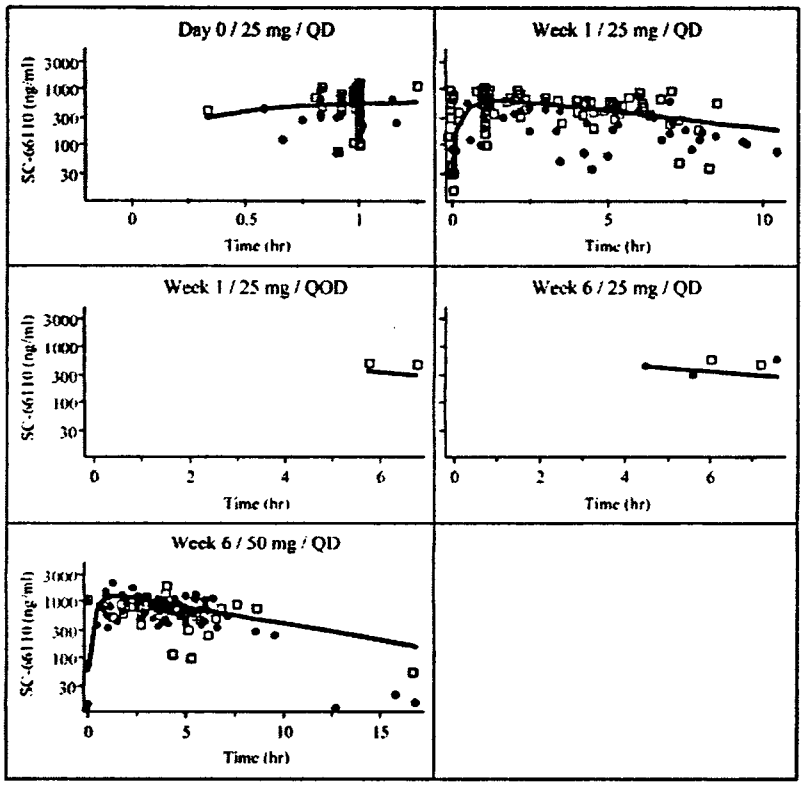
Table 4. Results of the secondary stepwise model building procedure.

Step[a]	Covariate	ELS	ΔELS (p-value)
0	Base Model	-62.744	--
1	SGOT – CL/F	-77.128	14.384 (<0.0002)
2	Age – V/F	-83.911	6.783 (0.0092)
3	Diabetes – CL/F	-90.236	6.325 (0.0119)
4	Weight – V/F	-95.925	5.689 (0.0171)
5	Sex – V/F	-105.558	9.633 (0.0019)
-1	Diabetes – CL/F	-98.768	6.790 (0.0092)
Final	SGOT – CL/F	-85.385	13.383 (0.0003)
	Age – V/F	-89.024	9.744 (0.0018)
	Weight – V/F	-89.180	9.588 (0.0020)
	Sex – V/F	-89.424	9.344 (0.0022)

[a]For each step, 1-5, the covariate parameter with the greatest ΔELS≥χ^2(1,0.025)=5.03 was reported and included in the model in the next step. For step –1, the covariate parameter with the smallest ΔELS≤ χ^2(1,0.005)=7.88 was eliminated. The covariates in the final step were included in the final model since their ΔELS>7.88.

Thus, the final model correlated SGOT with CL/F and age, weight, and sex with V/F. Figure 4 plots the base model prediction and stratifies the data by SGOT values above and below the median.

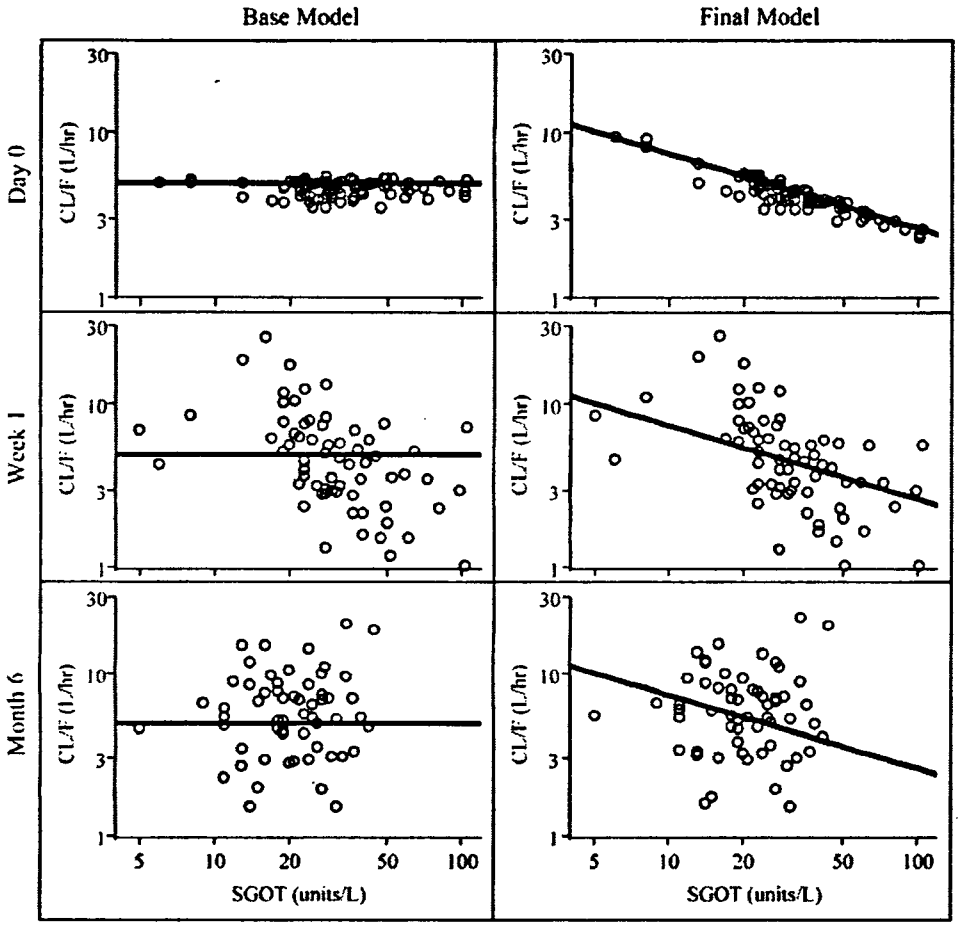
Figure 4. Observed Eplerenone Concentrations and the Conditional Base Model Prediction Stratified by SGOT (Median=25 units/L)



At Week 1, much of the data above the median are shown to be above the base model prediction. This result is consistent with the higher prediction of CL/F for lower SGOT.

Figure 5 displays the CL/F predictions (L/hr) for each individual by visit. The solid lines represent the population mean prediction of CL/F for the base and final models, respectively, as a function of SGOT.

Figure 5. CL/F Bayes Predictions versus SGOT for Each Individual By Visits for the Conditional Base Model and Conditional Final Model



The sponsor graphically explored the model prediction and observed data for eplerenone stratified above or below the median for age, weight, and gender. The base conditional model predicted V/F to decrease proportionally with age (older patients would have shorter terminal phases, t1/2=log(2)*V/CL). The model suggests that V/F increases nearly proportional to weight (heavier patients have longer terminal phases). Inspection of these plots does not reveal clear trends substantiating the assertions above. The final model also predicts that males have lower V/F than females of similar weight suggesting that males have a shorter apparent terminal phase.

Conditional Final Model

Conditional base and final model parameters compare in the Table 5.

Table 5.

	Base Model		Final Model	
Parameter	Estimate ± SE	IIV (IOV) %CV	Estimate ± SE	IIV (IOV) %CV
Tlag (hr)	0.0 ± NA	0 (0)	0.0 ± NA	0 (0)
ka (1/hr)	1.73 ± 0.42	134 (0)	1.61 ± 0.27	117 (0)
CL/F (L/hr)	4.88 ± 0.38	0 (69.1)	4.91 ± 0.35	0 (65.1)
SGOT	0		-0.448 ± 0.111	
V/F (L)	35.0 ± 2.9	0 (0)	39.7 ± 3.9	0 (0)
Age	0		-0.804 ± 0.278	
Weight	0		0.798 ± 0.262	
Sex	1		0.717 ± 0.086	
σ (~%CV)	28.0 ± 3.4		26.3 ± 3.1	

The sub-model equations were as follows:

$$Tlag = \theta_1 \quad [3]$$

$$ka_i = \theta_2 \exp(\eta_i^{ka}) \quad [4]$$

$$CL/F_{ij} = \theta_3 \left(\frac{SGOT}{25\,(\text{units/L})} \right)^{\theta_8} \exp(\eta_i^{CL} + \kappa_{ij}^{CL}) \quad [5]$$

$$V/F = \theta_4 \left(\frac{age}{65\ \text{yrs}} \right)^{\theta_7} \left(\frac{weight}{70\ \text{kg}} \right)^{\theta_6} \theta_9^{sex} \quad [6]$$

where sex was coded as 0 for females and 1 for males.

The final model parameter estimates suggest an inverse effect of SGOT on CL/F such that a 100% increase in SGOT results in a 27% decrease in CL/F. Age (weight) was predicted to decrease (increase) V/F nearly proportionally. Males were predicted to have 28.3% smaller V/F compared to females with similar age and weight. The inclusion of SGOT on CL/F decreased the IOV variability by 4%.
Model stability was tested with the nonparametric bootstrap procedure.
The bootstrap results (Table 6) were similar to the final model parameter estimation for all the parameters except SGOT.

Table 6.

Conditional Final Model Parameter Estimates and Bootstrap Results

	Final Model	Bootstrap Results	
Parameter	Estimate ± SE	Estimate ± SE	95% CI
ka (1/hr)	1.61 ± 0.27	1.97 ± 0.51	1.11 - 3.14
CL/F (L/hr)	4.91 ± 0.35	5.15 ± 0.72	3.81 – 6.81
SGOT	-0.448 ± 0.111	-0.255 ± 0.190	-0.609 – 0.114
V/F (L)	39.7 ± 3.9	37.6 ± 4.53	32.0 – 51.4
Age	-0.804 ± 0.278	-0.790 ± 0.326	-1.49 – -0.161
Weight	0.798 ± 0.262	0.990 ± 0.391	0.398 – 1.99
Sex	0.717 ± 0.086	0.709 ± 0.100	0.514 – 0.906
σ (~%CV)	26.3 ± 3.1	25.8 ± 3.3	19.1 – 32.3

The bootstrap estimates this parameter at 56% of the final model estimate. Furthermore, the bootstrap confidence interval includes 0, which indicates that the parameter may not be a significant predictor of CL/F. This discrepancy may suggest that a few observations were outliers. The bootstrap estimates of the absorption rate were about 22% greater than the final model, a result most likely due to the difficulty in characterizing the absorption phase with this design and perhaps due to the skewed nature of the ka Bayes predictions. With respect to the inference on the V/F covariate parameters, the bootstrap procedure bounds the parameters away from their null value (0.0 for age and weight and 1.0 for sex) concluding the same significance as the likelihood based stepwise procedures.

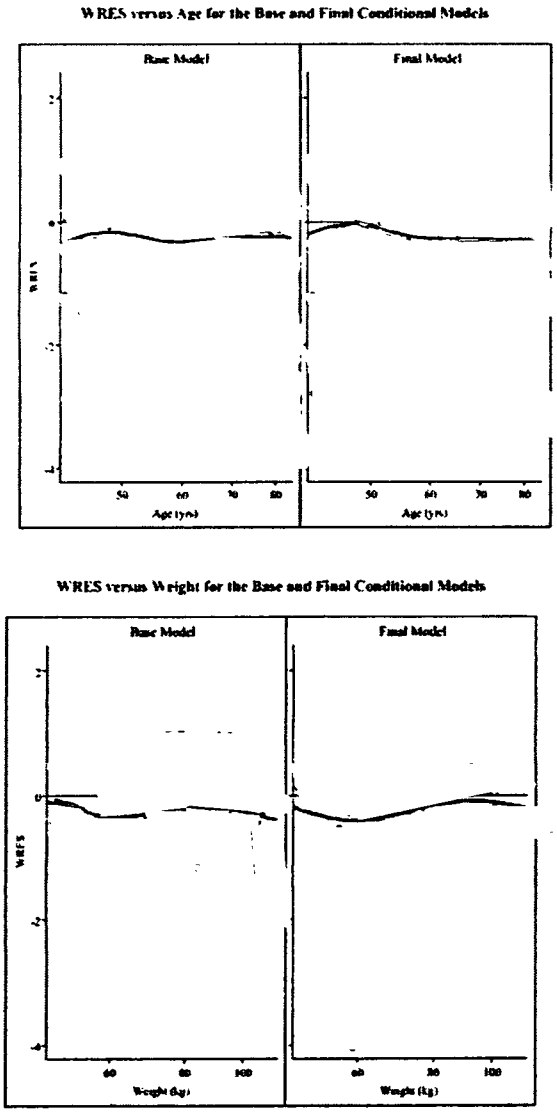


Figure 7. WRES vs weight (lower panel) and WRES vs age (upper panel) for the base and conditional models.

The WRES plots vs the covariates (Figure 7) in the final model were skewed and not much improvement can be seen in comparison to that in the base model. Therefore, the sponsor properly concluded that the fit to the data may not represent the best prediction of the data's central tendency.

Model Validation

The conditional model described above was unable to account for the aberrant lag-times. Since, the veracity of the data with the aberrant lag-times could not be discounted, the conditional model can't be used to predict the general heart failure population's pharmacokinetic profile. The sponsor did not perform the validation of the model.

Comparison with Healthy Volunteers, Black/Caucasian Hypertensives, and Patients Diagnosed with Congestive Heart Failure

The parameter estimates in Table 6 for CL/F (4.91 L/hr) were 55% less than the 10.8 L/hr estimated for healthy volunteers and 32% than that estimated for the Black/Caucasian hypertensive patients of IE3-01-08-020. The plasma concentrations were higher in the CHF patients than in the healthy volunteers, which is consistent with the patients lower estimate of apparent clearance. The 95% confidence interval for CL/F in CHF patients (Table 6) does not contains the hypertensive CL/F. The elderly patients' (study NE3-01-06-028) estimate (N=24) of CL/F was 6.60 L/hr. This estimate is contained within the 95% bootstrap confidence interval reported in Table 6. The age distribution for the CHF patients is greater than the hypertensive patients of IE3-01-08-020 (median age of 52.5). The model estimate of 4.91 L/hr (CI 3.81-6.81 L/hr) for CL/F in this substudy is comparable with the mean of 5.36 L/hr (geometric mean, determined at steady-state after 5 days of dosing) determined in a PK study of eplerenone in CHF patients (NE3-03-06-058).

CONCLUSIONS

The population mean estimate of CL/F reported in HF patients is less than that determined in young healthy volunteers, but is similar to elderly healthy volunteers, and patients diagnosed with CHF (NYHA II-IV). The pharmacokinetic parameter of CL/F was influenced only by SGOT. The sponsor speculated that this evidence was conflicting and the potential influence of SGOT was found to be small and clinically unimportant. The variability in lag-times is difficult to interpret. No clear pattern in the lag-times emerges to explain their cause. Several factors can be hypothesized to contribute to the excessively long absorption lag- times. Inaccurately recalled dose times, mishandling or confusion of samples, or time- varying covariates (not measured) that influence absorption are possibly explanations. Overall, insufficient information in the data exists to draw conclusions on the cause of the long lag-times.
The population mean CL/F and V/F estimates could be accurate for the general population provided that the lag-time issues are not due to any change in the bioavailability (F) within the patient. The sponsor admitted that skewed WRES and

Bayes predictions of the variance components indicates the population mean (typical value) fit to the data may not represent the best prediction Nevertheless, the consistency in CL/F in heart failure patients was found with the elderly healthy volunteer population. Additionally, the estimated apparent volume values 39.7 L were similar to the same estimated for adults (FDA review), 37.2 L. In this study, age, weight, and gender have an influence on V/F.

Comments:

1. In general, the parameter estimations obtained as a result of the population PK modeling were similar to the parameter estimations obtained from the rich data file for the CHF patients. However, several steps in this data analysis are not very convincing. The data censoring based on the different absorption lag-times and covariate analysis does not seem reasonable. The sponsor did not perform any model validation.
2. The population mean values of clearance of 4.9 L/hr were similar to the reported previously clearance values for geriatric patients (6.4 L/hr). Since the geriatric patients did not require the dose adjustment for eplerenone, there is no safety issue for the dose adjustment for the CHF patients.

18 pages redacted from this section of the approval package consisted of draft labeling

6.3 Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-437	Brand Name	Inspra
OCPB Division (I, II, III)	DIV-1	Generic Name	Eplerenone
Medical Division	CARDIORENAL	Drug Class	Blocker of aldosterone binding with mineralocorticoid receptors
OCPB Reviewer	ELENA MISHINA	Indication(s)	
OCPB Team Leader	P. Marroum	Dosage Form	25 mg, 50 mg, 100 mg tablets
		Dosing Regimen	25 mg QD for the initial dose which may be titrated up to 50 mg QD
Date of Submission	April 7 2003	Route of Administration	ORAL
Estimated Due Date of OCPB Review		Sponsor	Pharmacia
PDUFA Due Date		Priority Classification	S
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	1		
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	X	2		

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	Are the pharmacokinetics of eplerenone in patients with symptomatic heart failure comparable with the same in healthy volunteers?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-437, HFD-850(Lee), HFD-860(Marroum, Mehta, Mishina), Biopharm (CDER)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Elena Mishina
9/3/03 03:30:34 PM
BIOPHARMACEUTICS

Patrick Marroum
9/4/03 09:24:08 AM
BIOPHARMACEUTICS