



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION (Addendum)

NDA #: 20-386
SERIAL #: SE1-S028
DRUG NAME: COZAAR (Losartan Potassium) tablets
INDICATION: Renal Protection
SPONSOR: Merck & Co., Inc.

DOCUMENT REVIEWED:

1. Vols. 1 and 2 (CDER REC'D Date: November 13, 2001)
2. SAS data base in EDR

STATISTICAL REVIEWER: H.M. James Hung, Ph.D. (HFD-710)

MEDICAL REVIEWER: Juan Carlos Pelayo, M.D. (HFD-110)

PROJECT MANAGER: Sandra Birdsong (HFD-110)

STATISTICAL KEY WORDS: Interim analysis, DSMB, sample size change, log rank test, O'Brien-Fleming boundary, Cox regression, geographical region

Distribution: NDA 20-386, SE1-S028

HFD-110/Dr. Throckmorton
HFD-110/Dr. Stockbridge
HFD-110/Dr. Pelayo
HFD-110/Ms. Birdsong
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/chron

JHung/301-594-5436/DB1/cozaar.doc/4-1-2002

SUMMARY

This addendum is to remove the p-values of the component events (doubling serum creatinine, ESRD or death) as the “first” event of the primary composite endpoint, given in Table 1 of my review of March 1, 2002. The removal is to avoid possible misinterpretation of these p-values which originally were provided purely for the description purpose, not for statistical testing. As the result, Table 1 in the original review is changed to Table 1a give below.

Table 1a. Incidence of adjudicated primary events (Reviewer’s Analysis)

	Losartan (N=751)	Placebo (N=762)	Hazard ratio (95.2% CI)	p-value ^{\$}
Primary event				
Doubling serum creatinine, ESRD or death	327 (43.5%) Median time = 1303 days	359 (47.1%) Median time =1373 days	0.84 (0.72, 0.97)	0.022
Decomposition of the 1st primary event				
Doubling of SC	162 (21.6%)	198 (26.0%)	0.75 (0.61, 0.92)	
ESRD	64 (8.5%)	65 (8.5%)	0.93 (0.65, 1.31)	
Death	101 (13.5%)	96 (12.6%)	0.98 (0.74, 1.30)	
1st component endpoint				
Doubling of SC	162 (21.6%)	198 (26.2%)	0.75 (0.61, 0.92)	0.006
ESRD	147 (19.5%)	194 (25.5%)	0.71 (0.57, 0.89)	0.002
Death	158 (21.0%)	155 (20.3%)	1.02 (0.81, 1.27)	0.88
ESRD or death	255 (34.0%)	300 (39.4%)	0.80 (0.68, 0.95)	0.009

\$ nominal p-value, pre-specified primary analysis (Cox model using geographical region as covariate and baseline proteinuria as a stratification variable)

As said in the conclusion section of my review of March 1, 2002, there was some evidence that losartan might reduce the incidence of the primary composite endpoint, doubling of serum creatinine, ESRD or death, (reduction of risk = 16% with 95% CI of 3% to 28%, p = 0.022). The strength of evidence did not meet the usual standard of statistical evidence, at least lower by an order of magnitude in p-value. Approximately a half of the primary composite events were doubling of serum creatinine and the other half were ESRD or death as the first event. The treatment difference seemed to be largely shown by doubling of serum creatinine. However, in the patients with doubling serum creatinine, 51% developed ESRD in the losartan group and 65% in the placebo group; mean time from doubling serum creatinine to ESRD was about 30 days longer in the losartan group in these patients. In addition, during the study period, 19.5% of the losartan patients and 25.5% of the placebo patients developed ESRD; thus, losartan appeared to give a 29% reduction in risk of having an ESRD (p = 0.002). There is little difference in death rate between the losartan group and the placebo group.

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

/s/

James Hung
4/1/02 01:58:34 PM
BIOMETRICS
urgent attention needed

George Chi
4/1/02 02:22:15 PM
BIOMETRICS