Draft Minutes
Cardiovascular and Renal Drugs Advisory Committee Advisory Committee Meeting Dated: April 12, 2002

On Friday, April 12, 2002, the 96th meeting of the Cardiovascular and Renal Drugs Advisory Committee was held. Ten of the eleven members of the committee attended the meeting; the committee was supplemented with two consultant/SGEs, Dr. Jeffrey Kopp (a nephrologist) and Dr. Andrew Brem (a pediatric nephrologist). The Advisory Committee Members, SGE Consultants and sponsor received background packages (both FDA and sponsor) prior to the meeting. Twenty-four hours prior to the meeting, the background packages were posted to the FDA dockets web-site.

This meeting was held at the Holiday Inn, Silver Spring, Maryland. In attendance were approximately 200 people. The topic of the meeting was:

NDA 20-386/S028, Cozaar™ (losartan potassium), Merck and Company, Inc.

Proposed Indication: for the treatment of type II diabetic patients with nephropathy

Dr. JoAnn Lindenfeld, was the committee reviewer for the application. There were no Open Public Hearing speaker presentations or submissions.

The sponsor, Merck and Company, Inc., was the sole presenter at the meeting.

Sponsor's Presentation

Introduction	Michael C. Elia, Ph.D. Director, Regulatory Affairs Merck Research Laboratories
Background, Rationale and Results of the RENAAL Study	Shahnaz Shahinfar, M.D. Senior Director, Cardiovascular Clinical Research Merck Research Laboratories
Review of the Evidence and Conclusions	William Keane, M.D. Vice President, Clinical Development Merck - US Human Health Division

During the meeting, the Committee discussed issues related to the background packages and the sponsor presentation:>. The meeting concluded with the committee discussion of the questions. The committee formally voted on Questions Number: 5, **8, 9.1, 9.2.1, and 10.** The Questions, and vote where taken, are presented below.

FDA Questions to the Cardiovascular and Renal Drugs *Advisory Committee:*

\The Cardio-Renal Advisory Committee is asked to opine on the benefits and risks of losartan, an angiotensin II receptor antagonist, for the treatment of nephropathy in type 2 diabetes. Reviews of chemistry, pharmacology, toxicology, biopharmaceutics, biometrics, and clinical safety present no apparent barriers to its approval.

The Committee is asked if it believes the strength of evidence for a treatment benefit supports approval.

The direct evidence is derived from one study. RENAAL enrolled 1513 subjects with type 2 diabetes, hypertension,, proteinuria (albumin:creatinine _>300 mglg), and serum creatinine between 1.5 and 3 mgldL. Subjects were randomized to placebo or losartan (titrated as tolerated from 50 mg to 100 mg) and followed for a mean of 2.4 years. The primary end point was a time to first event comparison of losartan and placebo for death, end stage renal disease, or doubling of serum creatinine. The result was an estimated risk reduction of 16% (p=0.022), with treatment groups diverging after about 6 months.

1. There were 686 total end point events in the placebo and losartan groups, 32 fewer in the losartan group than on placebo. One of the characteristics of a none-too-small p-value is that the result is sensitive to the handling of subjects with incomplete data. In RENAAL, there were no subjects randomized but not treated, no subjects with questioned event adjudication, and no subjects lost to follow-up for end stage renal disease or mortality.
   1.1 Four hundred and sixty-three subjects discontinued study drug.
      1.1.1 How were they handled?
      1.1.2 How should they have been handled?
   1.2 at effect did the sponsor's rules for handling dropouts have on the credibility of the principal fmding?

   The consensus of the committee was that the sponsor 's rules for handing dropouts had no effect on the credibility of the principal finding.

2. Of the 686 primary end point events on placebo or losartan, 52% were creatinine elevation and 48% were death or need for dialysis. All of the treatment difference was the effect on creatinine.
   2.1 Was this a statistical anomaly?
   2.2 Was this because there were just so few clinical outcome events?
   2.3 Was this because the effects on clinical outcome would not be expected over 54 months of follow-up?
   2.4 Was this because an effect on serum creatinine is a poor predictor of clinical outcome?
   2.5 Subjects who experienced doubling of serum creatinine could later have end-stage renal disease or die. When these events are counted, the relative risk of death on losartan was 1.02 (95% CI 0.81-1.27) and the risk of needing dialysis was 0.71 (95% CI 0.57-0.89). Are these data supportive of an effect on clinical outcome?

3. In RENAAL, the mean blood pressure was significantly lower in the losartan group than in the placebo group.
   3.1 How does one know that blood pressure alone was not responsible for losartan's treatment effects?
   3.2 Is the mechanism of the treatment effect relevant to the description of the trial outcomes?

   The consensus of the committee was that it is difficult to establish the effect of blood pressure in this trial and thus the effect would be unknown. Furthermore, even though this effect is unknown, the general belief of the committee was that the treatment effect was not based solely on blood pressure effect.

4. Comment on other secondary end point in RENAAL.

4.1 There was a prespecified analysis of time to first cardiovascular death, non-fatal MI, hospitalization for CHF or unstable angina, stroke, or coronary or peripheral revascularization. There were 515 such events, with no significant difference in the distribution between groups.

4.1.1 Is this evidence of a lack of clinical benefit?

4.1.2 Is it comforting that there is a lack of apparent harm?

4.1.3 Were there simply too few events to show a meaningful effect?

In general, the committee believed that not much evidence could be gathered from the secondary endpoints because there were too few events, the study was not of sufficient duration and the population studied was not at sufficient risk However, the committee generally felt that the study revealed no evidence of clinical harm with regard to cardiovascular outcomes. At the same time, the Committee felt it was important to note that the study was not sufficiently powered to detect cardiovascular events, either beneficial or non-beneficial.

4.2 Proteinuria, assessed as mg per gram of creatinine, was lower on losartan at all times after baseline. Additionally, the rate of loss of renal function, assessed by the slope of reciprocal of the serum creatinine over time, was significantly lower, by about 13%, in the losartan group. at do these results contribute to the confidence one has in the clinical benefits of losartan in RENAAL?

In general', the committee believed that the results added to their confidence regarding the beneficial effects seen with losartan. Further, they agreed that these results were consistent with the plausible mechanism of action of the renal benefits.

5. Are the results of RENAAL *alone an* adequate basis for approval of losartan for the treatment of type-2 diabetic nephropathy?

VOTE: YES: 4 NO: 7 ABSTAIN:0

Concern was raised that approval was being requested based on a single study with a marginal "P" value. The committee also raised concern with the number ofpatients on losarten who experienced elevated potassium values during the study.

A drug with a related mechanism of action, captopril, has an indication for diabetic nephropathy in patients with type 1 diabetes. The primary basis of that approval was the demonstration, in a 409-subject, 2-year study, of 51% reduction ($p^{=}0.004$) in risk of doubling serum creatinine alone, and a 50% reduction ($p^{=}0.006$) in risk of mortality or end-stage renal disease. Both effects were manifest in the first few months of treatment. Captopril also reduces the progression for microalbuminuria to overt proteinuria.

6. Are the results with captopril germane to a discussion of losartan? In particular... 6.1
... is nephropathy in type 1 diabetes enough like nephropathy in type 2 diabetes? 6.2
...are the phamarmacological effects of captopril and losartan adequately similar?

The consensus of the committee was that types 1 and 2 diabetic nephropathy are similar enough for the study results of the captopril study to be germane. However, while the disease states might be similar, the two drugs are sufficiently different pharmacologically that it would be difficult to extrapolate data from studies in one class to the other.

7. If the results with captopril are relevant to losartan...

7.1 ... are the results on protein excretion similar with respect to direction and magnitude for captopril and losartan?

7.2 ... are the results on doubling of creatinine similar with respect to direction and magnitude for captopril and losartan?

7.3 ... are the results on death or ESRD similar with respect to direction and magnitude for captopril and losartan?

8. Are the results of RENAAL, *and prior expectations derived from the captopril database an* adequate basis for approval of losartan for the treatment of type-2 diabetic nephropathy?

VOTE: YES:4 NO: 7 ABSTAIN:0

9. In considering the approval of irbesartan for diabetic nephropathy, the Advisory Committee expressed interest in the program for losartan. The respective sponsors now have reciprocal agreements allowing reference to IDNT and RENAAL in support of one mother's programs.

9.1 Do the findings of IDNT support the effectiveness of losartan for diabetic nephropathy?

VOTE: YES: 10 NO: 1 **ABSTAIN:0**

9.2 Are the findings of IDNT as persuasive for losartan as would be...

9.2.1 ...replication of RENAAL?

VOTE: YES:0 NO:11 **STAIN:0**

9.2.2 ...beating an active control arm in RENAAL?

9.2.3 .. .a second study demonstrating losartan slows progression from microalbuminuria to proteinuria?

10. Should losartan be approved for the treatment of nephropathy in type 2 diabetes?

VOTE: YES:8 NO: 3 **ABSTAIN:0**