DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 3 2010

Anil K. Mandal, M.D.
240 Southpark Circle East
St. Augustine, Florida 32086

Re: Docket No. FDA-2006-P-0008

Dear Dr. Mandal:

This letter responds to your citizen petition received by the Food and Drug Administration (FDA) on September 6, 2006.[1] It also responds to the supplements you submitted on May 21, 2007, October 23, 2007, November 19, 2007, and January 15, 2008. Your petition requests that FDA restrict the use of or withdraw from the market angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) drug therapy in certain conditions because of an association with acute renal failure.

FDA has carefully considered the information submitted in your petition, supplements, and other relevant data available to the Agency. Based on our review of these materials, and for the reasons described below, your petition is denied.

I. BACKGROUND

ARBs and ACEIs are two drug classes indicated for the treatment of hypertension. Currently, several drug products in each of these drug classes are approved for the treatment of hypertension.[2] ARBs and ACEIs decrease the action of the renin-angiotensin aldosterone system by either interfering with the binding of the active endogenous compound angiotonin II to the receptors (ARBs) or inhibiting the generation of angiotensin II (ACEIs). In addition to an indication for treating hypertension, the labeling for some of these drug products states that they are indicated to prevent mortal or irreversible events or hospitalizations for patients with the following conditions:

- type 1 diabetes (captopril)
- type 2 diabetes (irbesartan and losartan),
- heart failure (enalapril and captopril)

[1] This citizen petition was originally assigned docket number 2006P-0351/CP1. The number changed to FDA-2006-P-0008 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] The following is a list of ARB drug products and FDA approval dates: candesartan (6/4/1998); eprosartan (12/22/1997); irbesartan (9/30/1997); losartan (4/14/1995); olmesartan (4/25/2002); telmisartan (11/10/1998); and valsartan (12/23/1996). The following is a list of ACE drug products and FDA approval dates: benazepril (6/25/1991); captopril (4/6/1981); enalapril (12/24/1985); fosinopril (5/16/1991); lisinipril (12/29/1997); moexipril (4/19/1995); perindopril (12/30/1993); quinapril (11/19/1991); ramipril (1/28/1991); and trandolapril (4/26/1996).

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- heart failure associated with acute myocardial infarction (captopril, trandolapril, lisinopril, enalapril, and candesartan)
- high risk of cardiovascular disease (ramipril)
- left ventricular hypertrophy (losartan)

The controlled clinical trials that supported the safety and efficacy of these drugs for such claims had adequate patient populations in the relevant condition to demonstrate that the treatment was safe and effective. The patient populations included many patients with diabetes mellitus and congestive heart failure, and receiving diuretic therapy; many patients were elderly.

II. DISCUSSION

Your petition asks FDA to withdraw ACEI and ARB drug products from the market or restrict their use for the following conditions or patient populations (referred to as *risk conditions* in this response):

(1) Diabetes mellitus with uncontrolled hyperglycemia
(2) Patients with diuretic therapy
(3) Diabetes mellitus with gastroparesis giving rise to vomiting
(4) Diabetic autonomic neuropathy with diarrhea
(5) Stable chronic renal failure in diabetic, hypertensive, or congestive heart failure patients
(6) Elderly patients
(7) Debilitated patients with tube feeding

You claim that the use of ACEI or ARB therapy in combination with the concomitant therapies or other risk conditions listed above increases the risk of acute renal failure (Petition at 2). You claim that sodium-volume depletion occurring with the risk conditions increases the risk of acute renal failure when ACEI or ARB therapy are added to treatment. In support of your claim, you described a chart review study of 74 patients — 41 who received an ACEI alone and 33 who received an ACEI in combination with diuretics. The article reported that patients treated with diuretics and ACEIs had increased serum creatinine levels compared to those treated with ACEIs alone. You also mention that you faxed 21 adverse event reports to MedWatch, FDA's system for healthcare workers and individuals to report adverse events (Petition at 3). You state that the sample of patients provides unequivocal evidence that ACEI or ARB therapy causes acute renal failure and the progression from stable chronic renal failure to end stage renal disease (ESRD) (Petition at 24). In addition, your petition described specific cases that you claim illustrate the problem of renal failure associated with ACEI or ARB treatment. In the supplements, you submitted additional information and data for patients who had adverse reactions to ACEI/ARB treatment.

You also assert that as a practitioner, you have not seen improvement or stabilization of renal function with the use of ACEI or ARB drug therapies (Petition at 25). You note that the ALLHAT study did not demonstrate a benefit of lisinopril (an ACEI drug

product) relative to chlorthalidone (a diuretic) in decreasing the development of end stage renal disease (Petition at 26).[3] In your supplement submitted on January 15, 2008, you enclose an editorial that concludes that there is not enough information on the long term safety of ACEI and ARB combination therapy in patients with stage 3 or 4 chronic kidney disease.

A. Data Do Not Indicate That These Products Should Be Removed or Restricted

We thank you for submitting your observations of adverse events associated with ACEI and ARB therapy. This anecdotal evidence, however, is inadequate to support your requested action. We disagree with your contention that ACEI and ARB drug therapies should be removed from the market or restricted because we believe that the net benefit of these drug products far exceeds the potential harm, even when used in the populations with the risk conditions you identify. Contrary to the information you submitted in your citizen petition and supplements, the clinical trial data support the safety and efficacy of ACEI and ARB drug products, including use in diabetic patients.

There is a vast controlled clinical trial experience demonstrating clinical benefits in preventing mortal and irreversible morbid events in many different patient populations. The at-risk patient populations that derived a benefit from these drug products are recognized in the indications for the products described in Section I. You suggest that any clinical benefit in the diabetic population reflects a better control of glucose levels, rather than treatment with ACEI or ARB drug products (Petition at 29-30), but that is not what the trials showed. Indeed, many uses of these products are specifically directed at patients with diabetes or who are receiving diuretic therapy. Other uses are directed at populations that include such patients.

Three placebo-controlled studies in diabetic patients provide clear evidence that ACEI and ARB drug products provide beneficial effects on renal function for these patients. In these studies, glucose control procedures were the same in both treatment groups, which differed only in whether patients received an ACEI or ARB, or received a placebo. As these were randomized studies, equivalent glucose control was presumably applied to both treatment groups. These studies, in patients with both type 1 and type 2 diabetes, indicated a benefit of drug treatment in delaying the time to doubling of serum creatinine levels or development of end-stage renal disease.

- The ***Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy***[4] was a randomized, placebo-controlled study in patients with insulin-dependent nephropathy. It was a multicenter, double-blind trial in which 409 patients, age 18-49 of either gender, with or without hypertension, with type 1

[3] The ALLHAT officers and coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288:2981-2997.

[4] Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. N Eng J Med. 1993; 329:20:1456-1462.

(juvenile type, onset before age 30) insulin-dependent diabetes mellitus, retinopathy, and proteinuria, were randomized to placebo or captopril (25 milligrams (mg), three times a day). To achieve blood pressure control, additional antihypertensive agents (diuretics, beta blockers, centrally acting agents, or vasodilators) were added as needed for patients in both groups. The approach to glucose control was based on the American Diabetes Association guidelines and glycosylated hemoglobin levels did not differ significantly between groups during the course of the study. The captopril group had a 51 percent reduction in risk of doubling of serum creatinine and a 51 percent reduction in risk for the combined endpoint of end-stage renal disease (dialysis or transplantation) or death. Captopril treatment resulted in a 30 percent reduction in urine protein excretion within the first 3 months, which was maintained throughout the trial. The captopril group had somewhat better blood pressure control than the placebo group, but the effects of captopril on renal function were greater than would be expected from the group differences in blood pressure reduction alone. Captopril was well tolerated in this patient population.

- The ***Irbesartan Diabetic Nephropathy Trial***[5] (IDNT) was a randomized, placebo- and active-controlled, double-blind, multicenter study conducted worldwide in 1,715 patients with type 2 diabetes, hypertension, and nephropathy. Patients were randomized to receive initially 75 mg of irbesartan (ARB), 2.5 mg of amlodipine[6], or matching placebo, each given once-daily and were then titrated to a maintenance dose of irbesartan 300 mg, or amlodipine 10 mg, as tolerated. Additional antihypertensive agents (excluding ACEI, ARB, and calcium-channel blockers) were added as needed to achieve a blood pressure goal for patients in all groups. The change in HbA_{1C} (a measure of glucose control) during the course of the study was similar for all treatments, indicating HbA_{1C} similar glucose control for these groups in the study.

  The primary composite endpoint was the time to occurrence of any one of the following events: doubling of baseline serum creatinine, ESRD (defined by serum creatinine $\geq$6 mg/deciliter (dL), dialysis, or renal transplantation) or death. Treatment with irbesartan resulted in a 20 percent risk reduction versus placebo ($p=0.0234$) and also reduced the occurrence of sustained doubling of serum creatinine as a separate endpoint (33 percent), but had no significant effect on ESRD alone. Follow-up of patients, however, showed a long-term decrease in ESRD in the irbesartan group. The secondary endpoint of the study was a composite of cardiovascular mortality and morbidity (myocardial infarction, hospitalization for heart failure, stroke with permanent neurological deficit, amputation). There were no statistically significant differences among treatment groups in these endpoints, indicating no adverse effect of irbesartan.

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[5] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Reproductive Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. N Eng J Med. 2001; 345:851-860.

[6] Amlodipine is a calcium channel blocker that was administered to assure that blood pressure control was similar so that outcomes could not be attributed to better blood pressure control.

- The ***Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan Study***[7] (RENAAL) was a randomized, placebo-controlled, double-blind, multicenter study conducted worldwide in 1513 patients with type 2 diabetes with nephropathy. Patients were randomized to receive 100 mg of losartan once daily or placebo on a background of conventional antihypertensive therapy, excluding ACEI and ARB drug products, and standard of care for the treatment of their diabetes. Because the study was designed to achieve equal blood pressure control in both groups, other antihypertensive agents (diuretics, calcium-channel blockers, alpha- or beta-blockers, and centrally acting agents) could be added as needed in both groups. Patients were followed for a mean duration of 3.4 years. The primary endpoint of the study was the time to first occurrence of any one of the following events: doubling of serum creatinine, ESRD (need for dialysis or transplantation), or death. Treatment with losartan resulted in a 16 percent risk reduction in this endpoint and also reduced the occurrence of sustained doubling of serum creatinine by 25 percent and ESRD by 29 percent. There was no effect on overall mortality.

In addition to the studies described above in diabetic populations, there are numerous studies of ACEIs in patients with heart failure, almost all of whom were receiving diuretics. ACEI use is, indeed, part of the standard treatment of heart failure, improving survival and decreasing hospitalization. The recent HOPE[8] and CHARM[9] studies further demonstrate the benefit of an ACEI in preventing mortal and morbid outcomes in an at-risk population for cardiovascular outcomes (HOPE) and of an ARB in a heart failure population (CHARM).

- The ***HOPE*** study was a large (9,541 patients), multicenter, randomized, double-blind study comparing ramipril and placebo in patients 55 or older who were considered at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that was accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria). Patients either had normal blood pressure or were under treatment with other antihypertensive agents. Patients were excluded if they had clinical heart failure or were known to have a low ejection fraction (<0.40). This study was designed to examine the long-term (mean of 5 years) effects of ramipril (10 mg orally once a day) on the combined endpoint of myocardial infarction, stroke, or death from cardiovascular causes.

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[7] Brenner BM, Cooper ME, DeZeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapnin SM, Zhang Z, Shahinfar S. Effects of Losartan on Renal and Cardiovascular Outcomes in Type 2 Diabetes and Nephropathy. N Eng J Med. 2001; 345:861-869.

[8] The Heart Outcomes Prevention Evaluation Study Investigators. N Eng J Med. 2000; 342:145-153.

[9] The two CHARM studies are: (1) Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Trial in Patients Intolerant of ACE-I. Granger CB, McMurray JJ, Yusuf S, et al. Lancet, 2003; 362:772-776 (CHARM-Alternative); (2) McMurray JJ, Ostergren J, Swedberg K. Lancet. 2003; 362:757-771 (CHARM-Added).

Approximately 38 percent of those enrolled into the HOPE study had a history of diabetes.

The **HOPE** study results showed that ramipril significantly reduced the rate of myocardial infarction, stroke, or death from cardiovascular causes (651/4645 vs. 826/4652, relative risk 0.78), as well as the rates of the three components of the combined endpoint. There was a major decrease in all cause mortality (12.2 percent for placebo to 10.4 percent for ramipril, $p = 0.0005$) and cardiovascular mortality (8.1 percent for placebo to 6.1 percent for ramipril, $p = 0.0002$).

Candesartan (an ARB drug product), was studied in two heart failure outcome studies: the CHARM-Alternative and the CHARM-Added study (for patients already receiving ACEI).

- Both the ***CHARM-Alternative*** and the ***CHARM-Added*** studies were international, double-blind, placebo-controlled trials in patients with New York Heart Association (NYHA) class II-IV heart failure and left ventricular ejection fracture (LVEF) < 40 percent. In both trials, patients were randomized to placebo or candesartan (titrated as tolerated to 32 mg once daily) and followed for up to 4 years. Patients with creatinine ≥ 3 mg/dL, serum potassium ≥ 5.5 milliequivalents (mEq)/L, symptomatic hypotension, or known bilateral renal stenosis were excluded. The primary end point in both trials was time to either cardiovascular death or hospitalization for heart failure.

  CHARM-Alternative included 2,028 subjects with NYHA Class II or III heart failure (mean ejection fraction 30%) who could not tolerate an ACEI. The mean age was 67 years. Sixty-two percent had a history of myocardial infarction, 50 percent had a history of hypertension and 27 percent had diabetes. Concomitant medications at baseline included diuretics in 85 percent of those enrolled. After a mean follow-up of 34 months, there was a 23 percent reduction in the risk of cardiovascular death or heart failure hospitalization on candesartan, with both components of the endpoint (either cardiovascular death or hospitalization for heart failure) contributing to the overall treatment effect.

  In the ***CHARM-Added*** study, 2,546 subjects with NYHA class II or III heart failure (mean ejection fraction 28%) who were receiving an ACE inhibitor were randomized to added candesartan or added placebo. The specific ACEI and dose were provided at the discretion of the investigators, who were encouraged to titrate patients to doses known to be effective in heart failure in clinical outcome trials. The mean age was 64 years. Fifty-six percent had a history of myocardial infarction, 48 percent had a history of hypertension, and 30 percent had diabetes. Diuretics were used in 90 percent of those enrolled in the study. After a median follow-up of 41 months, there was a 15 percent reduction in the risk of cardiovascular death or heart failure hospitalization on candesartan ($p=0.011$) with both components (either cardiovascular death or hospitalization for heart failure) contributing to the overall treatment effect.

With respect to the ALLHAT study, you suggest that it supports your request that ACEI and ARB drug products should be removed from the market in certain patient populations because it found no advantage of lisinopril over other antihypertensive drugs for most cardiovascular diseases and renal outcomes. We disagree with your analysis of the ALLHAT study. The population enrolled into the ALLHAT study was predominately a hypotensive population and all 4 treatments would be expected to be effective in preventing the consequences of elevated blood pressure so that it is not surprising that there was not a superior benefit of lisinopril. The lack of an effect in preventing end stage renal disease in a nondiabetic population is not pertinent to whether ACEI and ARB drug products should be removed from the market or restricted for the populations with the risk conditions. Furthermore, as noted above in the IDNT study, one ARB (irbesartan) was clearly superior to a calcium channel blocker (amlodipine) in delaying nephropathy.

B. Adequate Labeling Addresses Safety Concerns

It is, of course, recognized that in people whose renal function depends on high renin levels, ACEIs and ARBs can cause deterioration of renal function. At this time, we believe the precautionary statements in the current labeling for ACEI and ARB drug products are adequate to address your safety concerns regarding these drug products. The risk of deteriorating renal function in patients whose renal function depends on high renin, including dehydrated patients and patients on diuretics, is currently described in the labeling of ACEI and ARB drug products.

The current labeling for ACEI and ARB drug products contains language under the PRECAUTIONS section alerting the prescriber of the possibility of impaired renal function or hyperkalemia (often linked to renal dysfunction). For example, the following language is contained in the Micardis (telmisartan) labeling:

> ***Impaired Renal Function***: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) acute renal failure and/or death. Similar results may be anticipated in patients treated with MICARDIS tablets.
>
> In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of MICARDIS tablets in patients with unilateral or bilateral artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated.

In addition, labeling of several ACEI and ARB combination products containing diuretics contains a precautionary statement that renal dysfunction may result under certain circumstances. For example, the labeling for Prinzide (lisinopril and hydrochlorothiazide), an ACEI/diuretic combination product, contains the following language:

> *Impaired Renal Function*: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including lisinopril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.
>
> In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of lisinopril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.
>
> Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of lisinopril and/or discontinuation of the diuretic may be required.
>
> **Evaluation of the hypertensive patient should always include assessment of renal function.** (See DOSAGE AND ADMINISTRATION.)
>
> *Hyperkalemia:* In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1.4 percent of hypertensive patients treated with lisinopril plus hydrochlorothiazide. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. PRINZIDE should be used cautiously, if at all, with these agents and

with frequent monitoring of serum potassium. (See *Drug Interactions.*) . . .

Non-steroidal Anti-inflammatory Agents Including Selective Cyclooxygenase-2 (COX-2) Inhibitors: Reports suggest that NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of ACE inhibitors, including lisinopril. This interaction should be given consideration in patients taking NSAIDs or selective COX-2 inhibitors concomitantly with ACE inhibitors.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors, may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

These interactions should be considered in patients taking NSAIDS including selective COX-2 inhibitors concomitantly with diuretics and angiotensin II antagonists or ACE inhibitors. Therefore, the combination should be administered with caution, especially in the elderly.

In reviewing the patient case summaries you submitted, we found that the adverse events were adequately addressed by the drug product's labeling. A physician reading the drug product labeling would be aware of the risk of renal insufficiency and the need to monitor patients for renal function, and the possible need to adjust therapy if problems arose. For example, you describe the case of a 54-year old female with a history of hypertension, borderline diabetes, and congestive heart failure (Patient # 3, Petition at 7). She was treated with enalapril, spironolactone, and possibly oral potassium. Her serum creatinine was 2.5 mg/dL, and her potassium level (7.2 mEq/L) was potentially life threatening, with the very elevated potassium the result of the spironolactone. Upon discontinuation of both the enalapril and spironolactone, the potassium value and creatinine level decreased into the normal range. Subsequent ramipril and candesartan raised potassium to 5.4 (moderately elevated from normal) and increased creatinine to 1.7 mg/dL from 1.3 mg/dL. Upon discontinuation of ramipril and candesartan, her creatinine level measured about 1.5 mg/dL, slightly lower than the 1.7 on ACEI plus ARB.

We believe that this case demonstrates the well-recognized reversible, usually modest, increase in serum creatinine described in the current labeling for enalapril (an ACEI drug product). The elevated potassium reflect primarily the effect of the aldosterone blocker, with some contribution of the combined ACEI and ARB. The effect of those drugs on serum K is described in labeling.

III. CONCLUSION

For the reasons discussed above, your petition is denied. We do not believe that these drug products should be removed from the market for safety reasons, nor should they be restricted under the conditions you propose. Available data from large controlled trials demonstrate great benefits for these classes of drugs in preventing mortal and irreversible morbid events, and they do so in patients with the risk conditions you propose as criteria for not using the drugs. Furthermore, current labeling for these drug products is adequate to address your concerns regarding renal dysfunction.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research