DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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APR 3 2015

Sammy Almashat, M.D., M.P.H.
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Public Citizen
1600 20th Street, NW
Washington, DC 20009

Re: Docket No. FDA-2012-P-1053

Dear Drs. Almashat and Wolfe:

This letter responds to your citizen petition received on October 10, 2012 (Petition). In the petition, you state that using angiotensin-converting enzyme inhibitor (ACE inhibitor), angiotensin II receptor blocker (ARB), and aliskiren drug products together, in any combination, increases the risk of hyperkalemia, symptomatic hypotension, and renal dysfunction relative to therapy with a single product from these drug classes. You also assert that combination therapy confers no clinical advantage over monotherapy with an ACE inhibitor, ARB, or aliskiren drug product. You request that the Food and Drug Administration (FDA or Agency) take the following actions (Petition at 1-2):

(1) Add a boxed warning regarding the risks of combination therapy to the labeling for all medications that contain an ACE inhibitor, ARB, or aliskiren;

(2) Mandate the distribution of an FDA-approved Medication Guide for all medications that contain an ACE inhibitor, ARB, or aliskiren;

(3) Require all manufacturers of ACE inhibitor, ARB, and aliskiren drug products to distribute a Dear Health Care Provider letter; and

(4) Remove the text in the labeling for candesartan (an ARB) that indicates taking candesartan with an ACE inhibitor can reduce cardiovascular death and heart-failure hospitalizations more than an ACE inhibitor can alone.

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

I. BACKGROUND

A. ACE Inhibitors, ARBs, and Aliskiren

ACE inhibitors, ARBs, and aliskiren are classes of prescription drugs that act on the renin-angiotensin system (RAS). FDA approved the first product from these drug classes — the ACE inhibitor captopril — in 1981. The Agency has since approved several dozen more ACE inhibitor, ARB, and aliskiren drug products.[1] Each of the approved products is indicated for the treatment of hypertension. Several of the approved ACE inhibitor and ARB products are also indicated for the treatment of renal disease and cardiovascular (CV) disease.[2]

The effects of ACE inhibitor, ARB, and aliskiren drug products are primarily attributed to the products' inhibition of the RAS. The RAS regulates blood pressure and volume status and is an important etiologic factor in hypertension, renal disease, and CV disease. Chronic activation of the RAS is associated with vasoconstriction, vascular injury, atherogenesis, and inflammation. ACE inhibitor, ARB, and aliskiren drug products counter these effects by diminishing the activity of angiotensin II (ATII), the primary vasoactive hormone of the RAS. ACE inhibitors block the formation of ATII through inhibition of an enzyme, and ARBs block ATII from binding to its receptor. Aliskiren inhibits the activity of renin, an enzyme that forms a precursor to ATII.

As with any drug therapy, pharmacologic inhibition of the RAS has certain risks. For example, it is well established that inhibition of the RAS via monotherapy with an ACE inhibitor, ARB, or aliskiren drug product increases the risk of hyperkalemia, hypotension, renal dysfunction, and even renal failure in susceptible patients. Consequently, the labeling for every ACE inhibitor, ARB, and aliskiren drug product describes these adverse events and recommends periodic patient monitoring.

B. Combination Therapy and Dual Blockade of the RAS

Monotherapy with ACE inhibitor, ARB, and aliskiren drug products (i.e., RAS inhibitors) has been shown through clinical trials to be effective at treating hypertension, renal disease, and CV disease. It was hypothesized that using two RAS inhibitor drug products from different drug

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[1] The Prescription Drug Product List in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* publication, generally known as the Orange Book, identifies 48 products that contain either an ACE inhibitor, ARB, or aliskiren. Over half of the products are fixed dose combinations, and all but two of the products are available in multiple strengths. A complete list of all 48 ACE inhibitor, ARB, and aliskiren drug products is provided in the Appendix to this response.

[2] FDA has approved the following additional indications for the drugs noted in parentheses: asymptomatic left ventricular dysfunction (enalapril maleate); coronary artery disease (perindopril erbumine); heart failure (candesartan, captopril, enalapril maleate, fosinopril sodium, lisinopril, quinapril hydrochloride, trandolapril, and valsartan); left ventricular dysfunction post-myocardial infarction (captopril); nephropathy in Type 1 diabetics (captopril); nephropathy in Type 2 diabetics (irbesartan and losartan potassium); post-myocardial infarction (lisinopril, ramipril, trandolapril, and valsartan); reduced risk of CV events for high risk patients (telmisartan and ramipril); and reduced risk of stroke in patients with hypertension and left ventricular hypertrophy (losartan potassium).

classes concomitantly (i.e., "combination therapy") would be more effective than monotherapy at inhibiting the RAS, resulting in improved health outcomes for patients. Indeed, combination therapy with RAS inhibitors has been associated with greater blood pressure reduction and improved heart failure outcomes compared to monotherapy in some patient populations.

Nonetheless, combination therapy is less common than monotherapy with an ACE inhibitor, ARB, or aliskiren drug product. An analysis of health care claims data projected to the commercially insured population indicates that the number of patients on ACE inhibitor-ARB combination therapy was low in relation to the total number of patients that received prescriptions for ACE inhibitor or ARB drug products from outpatient retail pharmacy settings in 2011.[3] The projected data also show that the use of combination therapy is declining. Between 2008 and 2011, the number of patients in the commercially insured population on combination therapy fell by approximately 25 percent.[4] Recent published studies showing that combination therapy is not appropriate for many patients may be one factor in this decline.

C. Recent FDA Actions Related to Combination Therapy

1. Safety Review of Combination Therapy

The FDA began a review of safety issues associated with dual blockade of the RAS in 2011. We focused our analysis on data from the following trials: the Valsartan Heart Failure Trial (Val-HeFT);[5] the Valsartan in Acute Myocardial Infarction Trial (VALIANT);[6] the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Added Trial;[7] and the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET).[8] The basic design of these trials and the drug products that they studied are summarized below:

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[3] In 2011, approximately 29 million total patients received a dispensed prescription for an ACE inhibitor drug product, 12.5 million total patients received a prescription for an ARB drug product, and 450,100 total patients received a prescription for an aliskiren-containing product from U.S. outpatient retail pharmacies. IMS, Vector One®: Total Patient Tracker Database, Year 2011, Extracted 2013. Based on an analysis of health care claims data projected to the commercially insured U.S. population, 385,000 patients had overlapping concurrent prescription claims for both ACE inhibitor and ARB drug products in 2011. IMS LifeLink Health Plan Claims Database, Reporting Year 2011, Extracted 2013.

[4] IMS LifeLink Health Plan Claims Database, Reporting Years 2008-2011, Extracted 2013.

[5] Coh JN, Tognoni G. A randomized trial of the angiotensin receptor blocker valsartan in chronic heart failure. *NEJM* 2001; 345:1667-75.

[6] Pfeffer ME, McMurray JJ, Velazquez EJ. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *NEJM* 2003; 349:1893-1906.

[7] McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; 362:767-71.

[8] The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *NEJM* 2008; 358:1547–59.

Study	Basic Design	ARB	ACE Inhibitor
Val-HeFT	Val-HeFT was a double-blind trial conducted at 302 centers in 16 countries. A total of 5,010 patients age 18 or older with heart failure were enrolled. Patients were randomized to valsartan or placebo against a background of standard therapy for heart failure. The primary endpoints were all-cause mortality and heart failure morbidity, which was defined as the combination of cardiac arrest with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for 4 hours or more.	Valsartan	Use of any ACE inhibitor was permitted. Approx. 93 percent of enrolled patients were on background ACE inhibitor therapy.
VALIANT	VALIANT was a double-blind trial conducted at 931 centers in 24 countries. A total of 14,703 patients age 18 or older who had acute myocardial infarction with either signs of heart failure or evidence of left ventricular systolic dysfunction were enrolled. Patients were randomized to valsartan or captopril, or both. The primary endpoint was all-cause mortality.	Valsartan	Captopril
CHARM-Added	CHARM-Added was a double-blind trial conducted at 618 centers in 26 countries. A total of 2,548 patients with heart failure were enrolled. Patients were randomized to candesartan or a placebo against a background of standard therapy for heart failure. The primary endpoint was cardiovascular death or heart failure hospitalization.	Candesartan	Use of any ACE inhibitor was permitted. Over 99 percent of enrolled patients were on background ACE inhibitor therapy.
ONTARGET	ONTARGET was a double-blind trial conducted at 730 centers in 40 countries. A total of 25,620 patients over age 55 with coronary, peripheral, or cerebrovascular disease, or diabetes with end-organ damage were enrolled. The patients were randomized to telmisartan or ramipril, or both. The primary endpoint was the composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.	Telmisartan	Ramipril

The Agency completed its analysis of these trials' data in September 2011. We concluded that combination therapy is associated with increased rates of hyperkalemia, hypotension, and renal dysfunction compared to monotherapy.[9] Because the incidence of these adverse events was consistently higher in the combination therapy groups of all four trials, we determined that this finding is relevant to all ACE inhibitor-ARB drug combinations.[10]

In April 2012, FDA completed a review of the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE).[11] The ALTITUDE trial was a study of aliskiren versus placebo in addition to ACE inhibitor or ARB therapy in patients with type 2 diabetes and renal impairment, defined by either albuminuria or reduced glomerular filtration

[9] Rates of syncope, which might be caused by hypotension but also has other causes, were not found to be consistently higher with combination therapy.

[10] A specific precaution for combined use of telmisartan and ramipril was added to these drugs' labeling in 2009 based on the results of the ONTARGET trial, which found that combination therapy with telmisartan and ramipril was associated with higher risks of hyperkalemia, hypotension, and renal impairment than monotherapy. The ONTARGET trial did not demonstrate any benefit from combination therapy for the primary endpoint compared to monotherapy with ramipril.

[11] Parving HH, Brenner BM, McMurray JJV, et al. Cardiorenal endpoints in a trial of aliskiren in type 2 diabetes. *NEJM* 2012; 367:2205-2213.

rate (GFR). The trial was stopped prematurely because it failed to meet its primary efficacy endpoint (reduction in death, CV morbidity, and progression of kidney disease). Higher rates of hypotension, hyperkalemia, and renal impairment were observed in the aliskiren group compared to placebo. A higher incidence of CV outcomes (stroke and death) was also observed in the aliskiren group.

Most recently, FDA reviewed the results VA-NEPHRON study.[12] In this study, patients with type 2 diabetes and nephropathy were randomized to lisinopril (an ACE inhibitor) or placebo on top of background therapy with losartan (an ARB). The study was stopped early because of excess hyperkalemia and renal impairment in the combination therapy arm compared to the monotherapy arm and because of a lack of efficacy on the primary endpoint (decrease in GFR, end-stage renal disease, or death). The results of the VA-NEPHRON study are consistent with those of the ONTARGET and ALTITUDE trials.

2. Labeling Changes Related to Combination Therapy

Based on the results of the ALTITUDE trial, the labeling for aliskiren drug products was revised to caution against using them with ACE inhibitor and ARB drug products in patients with type 2 diabetes or renal impairment. Specifically, FDA requested that new drug application (NDA) holders add the following statements to the labeling for aliskiren drug products:

> Contraindication:
> *Do not use [aliskiren] with ARBs or ACE inhibitors in patients with diabetes.*
>
> Precaution:
> *Avoid use of [aliskiren] with ARBS or ACEI in patients with moderate renal impairment (GFR <60 ml/min).*

These statements were added to the labeling for every approved aliskiren drug product in April 2012[13] and have since been added to the labeling for 41 of the 44 approved ACE inhibitor and ARB drug products.

In June 2012, we took action to address the findings from our safety review of combination therapy. At that time, FDA requested that NDA holders add the following language to the DRUG INTERACTIONS section of the labeling for ACE inhibitor and ARB drug products:

> ***Dual Blockade of the Renin-Angiotensin System (RAS)***
> *Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in*

[12] Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *NEJM* 2013; 369:1892.

[13] As you note in the petition, we also issued a drug safety communication in April 2012 that highlighted the possible risks of using aliskiren concomitantly with ACE inhibitor or ARB drug products in patients with diabetes or renal impairment (Petition at 20). This communication is available at http://www.fda.gov/drugs/drugsafety/ucm300889.htm.

renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on <<drug>> and other agents that affect the RAS.

The labeling for 45 of the 48 approved ACE inhibitor, ARB, and aliskiren drug products now includes this "dual blockade" language.[14]

Finally, the labeling for RAS inhibitor products was revised in 2014 to reflect the findings from the VA-NEPHRON study. The following statement was added to the "dual blockade" language described above: "Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors." The labeling for 32 of the 48 approved ACE inhibitor, ARB, and aliskiren drug products has been updated with this statement.[15]

D. Safety-Related Product Labeling

1. Boxed Warnings

A boxed warning is the most serious warning that can be placed in the labeling for a prescription drug product. FDA regulations specify that a boxed warning must appear before anything else in a drug product's full prescribing information, and must contain, in uppercase letters, a heading that includes the word "WARNING" and other words that convey the general focus of information in the box (21 CFR 201.56(d)(1) and 201.57(c)(1)). In addition, a summary of the boxed warning must be included in the Highlights of Prescribing Information (21 CFR 201.56(d)(1) and 201.57(a)(4)).

Under 21 CFR 201.57(c)(1), FDA may require a boxed warning for certain contraindications or serious warnings, particularly those that may lead to death or serious injury.[16] We exercise this authority judiciously to preserve the impact and significance of boxed warnings. FDA has issued guidance that describes some common situations that may warrant a boxed warning.[17] However, every drug product is unique and raises different safety concerns, so our decisions regarding boxed warnings are made on a case-by-case basis.

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[14] The labeling for ramipril and telmisartan drug products contains slightly different language about dual blockade of the RAS that includes a discussion of the ONTARGET trial.

[15] The labeling for Atacand and Atacand HCT has different language about the risks and benefits of combination therapy because both products are indicated for use with an ACE inhibitor product to treat heart failure in adults with left ventricular systolic dysfunction. See section II.D. FDA is working with NDA holders and ANDA holder to bring the labeling for all approved ACE inhibitor, ARB, and aliskiren drug products up-to-date.

[16] See also 21 CFR 201.80(e).

[17] Guidance for Industry, *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011), available at http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf.

2. *Medication Guides*

A Medication Guide is FDA-approved patient labeling that conforms to the specifications in 21 CFR part 208. The Agency will require a manufacturer of a prescription drug product to develop a Medication Guide for distribution to patients if the product poses a serious and significant public health concern and we determine that patient labeling is necessary to ensure the safe and effective use of the product (21 CFR 208.1(a) and (b)).

To require a Medication Guide, the Agency must find that one or more of the three circumstances in 21 CFR 208.1(c) exists. The three circumstances are:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health, and patient adherence to directions for use is crucial to the drug's effectiveness.

As with boxed warnings, FDA's decisions to require a Medication Guide are made carefully and on a case-by-case basis.[18]

3. *Dear Health Care Provider Letters*

Dear Health Care Provider (DHCP) letters, informally known as "Dear Doctor" letters, are correspondence intended to alert physicians and other health care providers to important new or updated information about a drug. FDA regulations describe three types of DHCP letters: (1) Important Drug Warning letters, which disseminate information about a significant hazard to health associated with the use of a drug; (2) Important Prescribing Information letters, which announce important changes in drug package labeling; and (3) Important Correction of Drug Information letters, which correct misinformation in prescription drug advertising or labeling (21 CFR 200.5(c)). DHCP letters are often used to convey important safety information that is to be incorporated into the BOXED WARNINGS, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS section of a drug product's labeling.[19]

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[18] See Medication Guide Final Rule, 63 FR 66378 at 66379, December 1, 1998.

[19] See Guidance for Industry and FDA Staff, *Dear Health Care Provider Letters: Improving Communication of Important Safety Information* (Jan. 2014), available at http://www.fda.gov/downloads/Drugs/Guidances/ucm233769.pdf.

II. DISCUSSION

In the petition, you state that combination therapy with ACE inhibitor, ARB, and aliskiren drug products increases the risk of serious adverse events without any added clinical benefit, and that the warnings in the products' labeling are inadequate for safe use in virtually all patient populations (Petition at 23). Consequently, you request that the Agency take the following actions: (1) add a boxed warning to the labeling of every ACE inhibitor, ARB, and aliskiren drug product advising against using the products in combination; (2) require the distribution of an FDA-approved Medication Guide alerting patients to the risks of combination therapy; (3) mandate a DHCP letter that alerts physicians and other health care professionals to the risks of combination therapy and that provides instructions on optimal titration of ACE inhibitor, ARB, and aliskiren monotherapy; and (4) remove certain text in the candesartan labeling concerning the clinical effect of using the drug product with an ACE inhibitor (Petition at 23-24). We address each of your requests below.

A. Request to Add a Boxed Warning

You request that FDA require a boxed warning (also known as a "black box warning") for all medications containing ACE inhibitors, ARBs, and aliskiren, indicating that using products from these drug classes together, in any combination, provides no clinical benefit and increases the risks of hyperkalemia, symptomatic hypotension, and renal failure (Petition at 23). You propose the following text for the boxed warning (Petition at 24):

> **In several large, long-term studies, taking angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), or aliskiren together, in any combination, has been shown to result in an increased risk of kidney dysfunction, low blood pressure, and high blood potassium levels. These side effects are potentially life-threatening. Taking these medications in combination is no more beneficial than taking the drugs individually.**
>
> **Therefore, the combined use of ACE inhibitors [corresponding drug name, if ACE inhibitor], ARBs [corresponding drug name, if ARB], and aliskiren should be avoided in all patients. Any patient necessitating combination therapy after careful consideration should have renal function, blood pressure, and electrolytes regularly monitored.**

Your request for a boxed warning is based on the results of clinical trials that assessed the effects of combination therapy in patients with CV disease, heart failure, and renal disease.

As explained below, the labeling for ACE inhibitor, ARB, and aliskiren drug products has long-described the risks of hyperkalemia, hypotension, and renal dysfunction. We agree that combination therapy increases the risks of these adverse events,[20] but in our judgment the magnitudes of the increases are not significant enough to warrant a boxed warning advising against combination therapy. Rather, we believe that the current labeling for RAS inhibitor

[20] See section I.C.

products adequately addresses the risks of hyperkalemia, hypotension, and renal dysfunction in all patients, including those on combination therapy. Furthermore, based on our review of the available evidence, and contrary to what you assert, we believe that combination therapy results in clinical benefits for certain patients. Therefore, your request is denied.

1. The Current Labeling for ACE Inhibitors, ARBs, and Aliskiren Adequately Addresses the Risks of Combination Therapy

Your request for a boxed warning is based, in part, on alleged deficiencies in the existing labeling for ACE inhibitor, ARB, and aliskiren drug products. Specifically, you assert that combination therapy is addressed in the labeling for only six drug products and that the information in these products' labeling concerning the risks associated with combination therapy is "wholly inadequate" (Petition at 24).[21] You point to this inadequacy as a reason why the labeling for every approved ACE inhibitor, ARB, and aliskiren drug product should be revised to carry your proposed boxed warning (Petition at 24).

We disagree with your assessment of the labeling for ACE inhibitor, ARB, and aliskiren drug products. As explained in section I.C.2, the labeling for ACE inhibitor and ARB products was updated in 2012 to add information about the risks associated with combination therapy (i.e., dual blockade of the RAS). The labeling for most products was updated shortly before the date of your petition; thus you may not have been aware of all of these changes at the time the petition was submitted.[22]

Moreover, we believe that the current labeling for ACE inhibitor, ARB, and aliskiren drug products, including the recent updates to the products' labeling, adequately addresses the risks associated with combination therapy. In particular, the labeling changes described in section I.C.2 state that combination therapy results in a dual blockade of the RAS; that dual blockade of the RAS is associated with increased risks of hyperkalemia, hypotension, and renal dysfunction (including acute renal failure); and that the blood pressure, renal function, and electrolytes in combination therapy patients should be closely monitored. The information in your petition has not altered our view of the safety profile of combination therapy or persuaded us that further labeling changes are needed, much less a boxed warning.

In addition, we note that the labeling for ACE inhibitor, ARB, and aliskiren drug products has included warnings about hyperkalemia, hypotension, and renal dysfunction, since before the

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[21] According to the petition, combination therapy is addressed in the current labeling for the following six products: (1) aliskiren; (2) ramipril; (3) telmisartan; (4) valsartan; (5) candesartan; and (6) losartan (Petition at 20-22, 24).

[22] Before the date of your petition (October 4, 2012), FDA approved labeling supplements containing a statement about dual blockade of the RAS (see section I.C.2) for the following drugs: benazepril hydrochloride (9/21/2012); captopril (8/27/2012); enalapril maleate (9/13/2012); eprosartan mesylate (9/12/2012); irbesartan (9/12/2012); lisinopril (8/13/2012); losartan potassium (9/28/2012); moexipril hydrochloride (9/14/2012); olmesartan medoxomil (9/28/2012); quinapril hydrochloride (9/21/2012); and trandolapril (9/11/2012). Statements concerning dual blockade of the RAS were also added to the labeling for ramipril, telmisartan, and aliskiren drug products before October 4, 2012. However, because of special circumstances associated with these products, the statements in their labeling are slightly different from the class language described in section I.C.2.

labeling was revised to address these risks in the context of combination therapy. As discussed earlier in section I.A, hyperkalemia, hypotension, and renal dysfunction are all well-documented side effects of monotherapy that have been described in the labeling for these products for many years. For example, the PRECAUTIONS section of the labeling for the ACE inhibitor Vasotec (enalapril maleate) has included the following information on the risks of renal impairment and hyperkalemia since 1987:

> *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 VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril 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 VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of VASOTEC 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:* Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See *Drug Interactions.*)[23]

Statements concerning the risks of renal impairment and hyperkalemia have appeared in the labeling for every other ACE inhibitor and ARB drug product for similarly long periods of time.

Against this backdrop, we believe that the boxed warning you have proposed is unnecessary at this time. Rather, we believe that the current labeling for ACE inhibitor, ARB, and aliskiren drug products, as updated with the changes described in section I.C.2, adequately informs physicians of the risks associated with combination therapy.

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[23] See Vasotec labeling approved on January 28, 1987, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/018998_S006_Vasotec_APPROVAL_PACKAGE.pdf. The current labeling for Vasotec contains nearly identical language concerning the risks of renal impairment and hyperkalemia. See Vasotec labeling approved on December 24, 2014, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/018998s079lbl.pdf.

2. *Combination Therapy May Be Appropriate for Certain Patients*

In the petition, you assert that there is no patient population in which combination therapy confers clinical benefits relative to monotherapy (Petition at 23). You argue that the lack of clinical benefits, coupled with the increased risk of hyperkalemia, hypotension, and renal dysfunction, justifies your request that the risks of combination therapy be presented in a boxed warning.

The evidence does not support your assertion. Studies show that combination therapy with RAS inhibitors results in greater blood pressure lowering than does monotherapy.[24, 25] In addition, the CHARM-Added trial found that adding candesartan (an ARB) to ACE inhibitor therapy reduced the risk of the combined endpoint of CV death and heart failure hospitalizations in heart failure patients. Based on this evidence, FDA approved the addition of the following statement to the INDICATIONS AND USAGE section of candesartan's labeling: "Candesartan cilexetil tablets also have an added effect on these outcomes [of reducing cardiovascular death and heart failure hospitalizations] when used with an ACE inhibitor."[26]

In short, the available evidence indicates that for some patients, combination therapy may provide an added benefit over monotherapy with an ACE inhibitor, ARB, or aliskiren drug product. A boxed warning in the labeling for these products advising physicians that combination therapy "should be avoided in all patients" would therefore be inappropriate.

B. Request for a Medication Guide

You request that FDA require the distribution of an FDA-approved Medication Guide for all ACE inhibitor, ARB, and aliskiren drug products (Petition at 2, 24).[27] You state that the

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[24] Doulton TW, He FJ, MacGregor GA. Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. *Hypertension* 2005; 45: 880-6.

[25] The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *NEJM* 2008; 358:1547-59.

[26] We note that this statement is consistent with the 2013 ACCF/AHA Guideline for the Management of Heart Failure, which states that adding an ARB may be considered in persistently symptomatic patients with systolic heart failure who are already being treated with an ACE inhibitor and a beta blocker in whom an aldosterone antagonist is not indicated or tolerated. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;128:e240–e327. We acknowledge that the 2013 ACCF/AHA guideline recommends against routine combined use of ACE inhibitor and ARB drug products, and that the Eighth Joint National Committee (JNC8) guidelines for the management of high blood pressure also recommend against using an ACE inhibitor and ARB together in the same patient. See id.; James PA et al. 2014 Evidence-based guidelines for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee. *JAMA* 2014 Feb 5; 311(5):507. However, both the ACCF/AHA guideline and the JNC8 guidelines concede that there is insufficient evidence from randomized, controlled, clinical trials to support these recommendations.

[27] No approved ACE inhibitor, ARB, or aliskiren drug product has a Medication Guide. Seventeen products have a Patient Package Insert (PPI) – another form of FDA-approved patient labeling that must accompany a product's full prescribing information. Unlike Medication Guides, however, PPIs are not required to conform to the specifications in 21 CFR part 208.

Medication Guide should include a warning that combination therapy increases the risk of renal failure, symptomatic hypotension, and hyperkalemia, and provides no clinical benefit over monotherapy with any of the drug products (Petition at 24). You also state that the Medication Guide should be dispensed to patients before they receive their first dose of any ACE inhibitor, ARB, or aliskiren drug product (Petition at 24).

As explained in section I.D.2, the Agency must determine that one or more of the three circumstances described in 21 CFR 208.1(c) has been met before it can require a Medication Guide. We summarize below the applicability of each circumstance to your request for a Medication Guide.

> Circumstance (1): The drug product is one for which patient labeling could help prevent serious adverse effects.[28]

The serious adverse effects for which you request that FDA require a Medication Guide are increased risks of renal failure, symptomatic hypotension, and hyperkalemia. Patient labeling, however, is not likely to prevent increases in renal failure, symptomatic hypotension, and hyperkalemia because there is no specific preventive measure that can be taken by a combination therapy patient to decrease these risks. Hyperkalemia, hypotension, and renal dysfunction are not unique to combination therapy, but rather can be caused by many different health problems and drugs (including monotherapy with a RAS inhibitor product). Thus, discontinuing combination therapy will not necessarily reduce the risks of these adverse effects, and might actually result in harm to the patient.

> Circumstance (2): The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.[29]

Given the serious medical implications of untreated hypertension, and considering the potential benefits of combination therapy to heart failure patients, the health care provider is in the best position to educate patients about the risks and benefits of combination therapy. We note that the labeling for approved ACE inhibitor, ARB, and aliskiren drug products was recently revised to describe the risks associated with combination therapy.[30] Health care providers can consider this information and discuss combination therapy with the patient, taking into consideration the patient's medical history and individual physical condition. FDA has advised that "health care providers who directly communicate with patients are in the best position to educate patients by personalizing oral and written information."[31] We believe that the risk information provided in

[28] Drugs potentially falling into this category are those for "which there is a known 'risk control strategy'" or "where easily taken preventive measures can prevent harm." Medication Guide Final Rule, supra note 18 at 66388.

[29] Drugs potentially meeting this criterion are those for which "the risk . . . is relatively great, greater than a patient would anticipate given the relatively benign condition being treated . . . [or] where understanding the adverse effects is critical to a choice among alternative treatments with different safety and effectiveness profiles . . . ." Id.

[30] See section II.A.

[31] Medication Guide Final Rule, supra note 18 at 66384.

the revised labeling for approved ACE inhibitor, ARB, and aliskiren drug products, along with counseling by the health care provider administering the drug, are sufficient to allow the patient to make an informed decision whether to start, or to continue, combination therapy.

> Circumstance (3): The drug product is important to health, and patient adherence to directions for use is crucial to the drug's effectiveness.[32]

FDA is not aware of any issues concerning the ability of combination therapy patients to adhere to directions for use.

The Agency has determined, after considering the three circumstances described above, that a Medication Guide on the adverse effects associated with combination therapy is not necessary for patients' safe and effective use of ACE inhibitor, ARB, and aliskiren drug products. We therefore deny your request for a Medication Guide.

C. Request for a DHCP Letter

In the petition, you request that FDA mandate that manufacturers send a DHCP letter (which you refer to as a "Dear Doctor" letter) to physicians and other health care professionals alerting them that combination therapy increases the risk of certain adverse events with no added benefit over monotherapy. You also request that the letter include information about the optimal titration of ACE inhibitor, ARB, and aliskiren monotherapy (Petition at 2, 24).

We are not persuaded by the evidence cited in your petition that it is necessary to mandate the distribution of a DHCP letter about combination therapy with instructions on optimal titration of monotherapy. The purpose of a DHCP letter is to alert health care professionals to important new information about a drug.[33] As discussed in section II.A.1, the risks of hyperkalemia, hypotension, and renal dysfunction associated with monotherapy and combination therapy have been described in labeling for many years. Indeed, the downward trend in the number of patients using ACE inhibitor and ARB drug products together[34] suggests that physicians are generally aware of these risks and have been considering them in their prescribing decisions. Consequently, we decline to require that manufacturers disseminate this information to health care professionals via an Important Drug Warning letter or any other type of DHCP letter.

D. Request to Remove Text from the Labeling for Candesartan

You request the removal of the following statement in the INDICATIONS AND USAGE section of the candesartan labeling: "Candesartan cilexetil tablets also have an added effect on these outcomes [of reducing cardiovascular death and heart failure hospitalizations] when used with an ACE inhibitor" (Petition at 24). You imply that this statement should not have been included in

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[32] Drugs potentially falling into this category are those for which "nonadherence could compromise patients' health by interfering with effectiveness." Id. at 66388.

[33] See section I.D.3.

[34] See section I.B.

the labeling because it is based on a finding from the "non-standardized" CHARM-Added trial (Petition at 12-13, 21). You also claim that the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial[35] found no added benefit on CV death or heart failure hospitalizations when candesartan was added to standardized doses of the ACE inhibitor enalapril (Petition at 7-8, 24).

We do not agree that the "non-standardized" design of the CHARM-Added trial is a sufficient reason to disregard its finding that combination therapy provided added clinical benefits in heart failure patients.[36] At a meeting held on February 24, 2005, the Cardiovascular and Renal Drugs Advisory Committee extensively discussed whether this finding was valid given that neither the dose nor type of background ACE inhibitor therapy was standardized in the CHARM-Added trial. The Committee concluded that at the doses of ACE inhibitor therapy reached in the trial, it was evident that the addition of candesartan significantly reduced the risk of CV mortality and heart failure hospitalizations.[37] Consistent with the Committee's advice, FDA approved an indication for added benefit when candesartan is used with an ACE inhibitor therapy in heart failure patients. Additionally, we note that the newly updated ACCF/AHA Heart Failure Treatment Guidelines continue to recommend the addition of an ARB to ACE inhibitor therapy in certain heart failure patients.[38]

We also disagree that the results of the RESOLVD trial support your request to remove this indication from candesartan's labeling. The RESOLVD trial was smaller than the CHARM-Added trial and, as you suggest in the petition, was underpowered to detect whether the combination of candesartan and enalapril resulted in additional clinical benefits over monotherapy with either drug product (Petition at 7). We are not aware of any other trial that has produced results that conflict with those of the CHARM-Added trial, nor does the petition identify one.

For the reasons described, we do not believe the available evidence supports removing the indication for added benefit when candesartan is used with an ACE inhibitor therapy in heart failure patients. Accordingly, your request that we do so is denied.

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[35] McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study. *Circulation.* 1999; 100:1056-64.

[36] In the petition, you define a "standardized" clinical trial as a double-blinded trial in which (1) patients were randomized to one of three therapy groups (ACE inhibitor/ARB combination therapy, ACE inhibitor monotherapy, or ARB monotherapy) and (2) patients within a therapy group were assigned to receive the same ACE inhibitor and ARB medication at identical doses (Petition at 6). A "non-standardized" trial is any trial that does not meet these criteria.

[37] See Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting, February 24, 2005, available at http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4092M1_Final.htm.

[38] See section II.A.2.

III. CONCLUSION

As explained above, your petition is denied. We will continue to monitor the public literature and other relevant information sources for data related to the concomitant use of ACE inhibitor, ARB, and aliskiren drug products, and if necessary, we will take further action to address any safety concerns.

Sincerely,

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

APPENDIX

Approved ACE Inhibitor, ARB, and Aliskiren Drug Products through February 2015[1]

Proprietary or Established Name(s)	Active Ingredient(s)	Dosage Form	Initial Approval Date
ACE Inhibitor Products			
Capoten	Captopril	Tablet	04/06/1981
Captopril and Hydrochlorothiazide	Captopril; Hydrochlorothiazide	Tablet	10/12/1984
Vasotec	Enalapril Maleate	Tablet	12/24/1985
Vaseretic	Enalapril Maleate; Hydrochlorothiazide	Tablet	10/31/1986
Prinivil; Zestril	Lisinopril	Tablet	12/29/1987
Enalaprilat	Enalaprilat	Injectable	02/09/1988
Prinzide; Zestoretic	Hydrochlorothiazide; Lisinopril	Tablet	02/16/1989
Altace	Ramipril	Capsule	01/28/1991
Fosinopril Sodium	Fosinopril Sodium	Tablet	05/16/1991
Lotensin	Benazepril HCl	Tablet	06/25/1991
Accupril	Quinapril HCl	Tablet	11/19/1991
Lotensin HCT	Benazepril HCl; Hydrochlorothiazide	Tablet	05/19/1992
Aceon	Perindopril Erbumine	Tablet	12/30/1993
Fosinopril Sodium and Hydrochlorothiazide	Fosinopril Sodium; Hydrochlorothiazide	Tablet	11/30/1994
Lotrel	Amlodipine Besylate; Benazepril HCl	Capsule	03/03/1995
Univasc	Moexipril HCl	Tablet	04/19/1995
Mavik	Trandolapril	Tablet	04/26/1996
Tarka	Trandolapril; Verapamil HCl	Tablet, Extended Release	10/22/1996
Uniretic	Hydrochlorothiazide; Moexipril HCl	Tablet	06/27/1997
Accuretic	Hydrochlorothiazide; Quinapril HCl	Tablet	12/28/1999
Ramipril	Ramipril	Tablet	02/27/2007
Epaned Kit	Enalapril Maleate	For Solution	08/13/2013
Prestalia	Amlodipine Besylate; Perindopril Arginine	Tablet	01/21/2015

[1] Excerpted from the Prescription Drug Product List in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* publication.

Proprietary Name(s)	Active Ingredient(s)	Dosage Form	Initial Approval Date
ARB Products			
Cozaar	Losartan Potassium	Tablet	04/14/1995
Hyzaar	Hydrochlorothiazide; Losartan Potassium	Tablet	04/28/1995
Avapro	Irbesartan	Tablet	09/30/1997
Avalide	Hydrochlorothiazide; Irbesartan	Tablet	09/30/1997
Teveten	Eprosartan Mesylate	Tablet	12/22/1997
Diovan HCT	Hydrochlorothiazide; Valsartan	Tablet	03/06/1998
Atacand	Candesartan Cilexetil	Tablet	06/04/1998
Micardis	Telmisartan	Tablet	11/10/1998
Atacand HCT	Candesartan Cilexetil; Hydrochlorothiazide	Tablet	09/05/2000
Micardis HCT	Hydrochlorothiazide; Telmisartan	Tablet	11/17/2000
Diovan	Valsartan	Tablet	07/18/2001[2]
Teveten HCT	Eprosartan Mesylate; Hydrochlorothiazide	Tablet	11/01/2001
Benicar	Olmesartan Medoxomil	Tablet	04/25/2002
Benicar HCT	Hydrochlorothiazide; Olmesartan Medoxomil	Tablet	06/05/2003
Exforge	Amlodipine Besylate; Valsartan	Tablet	06/20/2007
Azor	Amlodipine Besylate; Olmesartan Medoxomil	Tablet	09/26/2007
Exforge HCT	Amlodipine Besylate; Hydrochlorothiazide; Valsartan	Tablet	04/30/2009
Twynsta	Amlodipine Besylate; Telmisartan	Tablet	10/16/2009
Tribenzor	Amlodipine Besylate; Hydrochlorothiazide; Olmesartan Medoxomil	Tablet	07/23/2010
Edarbi	Azilsartan Kamedoxomil	Tablet	02/25/2011
Edarbyclor	Azilsartan Kamedoxomil; Chlorthalidone	Tablet	12/20/2011
Aliskiren Products			
Tekturna	Aliskiren Hemifumarate	Tablet	03/05/2007
Tekturna HCT	Aliskiren Hemifumarate; Hydrochlorothiazide	Tablet	01/18/2008
Tekamlo	Aliskiren Hemifumarate; Amlodipine Besylate	Tablet	08/26/2010
Amturnide	Aliskiren Hemifumarate; Amlodipine Besylate; Hydrochlorothiazide	Tablet	12/21/2010

[2] Initially approved as a capsule on December 23, 1996. The capsule dosage form has since been discontinued.