DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 17 2003

James Feldman, MD FACEP
Department of Emergency Medicine
Boston Medical Center
818 Harrison Avenue
Boston, Massachusetts 02118

Re: Docket No. 02P-0374/CP1

Dear Dr. Feldman:

This letter responds to your citizen petition received on August 15, 2002, requesting that a *Black Box warning* be added to the labeling of Angiotensin Converting Enzyme Inhibitors (ACEIs or ACE inhibitors). In particular, you requested a Black Box warning regarding the risk of life-threatening angioedema. For the reasons stated below, your petition is denied.

I. BACKGROUND

ACEIs inhibit the enzymatic conversion of angiotensin I to angiotensin II, a hormone in the body that causes blood vessels to constrict. Since ACEIs first received FDA approval in the early 1980s, dozens of ACE inhibitors have been approved for a variety of indications such as hypertension, diabetic nephropathy, acute myocardial infarction, heart failure, and left ventricular dysfunction. In the year 2001 alone, over 100 million prescriptions were written for ACE inhibitors.[1]

While you acknowledged the effectiveness of ACEIs in your petition, you expressed concern regarding their association with angioedema. Specifically, you cited a number of cases from your personal experience and the medical literature in which life-threatening, and in some cases fatal, angioedema has been associated with ACEI use. Based on these cases, you requested that a Black Box warning be added to the labeling of ACE inhibitors.

As discussed in greater detail below, ACEI labeling already (1) warns physicians of the risk of life-threatening angioedema, (2) discusses the symptoms that should prompt patients to seek medical assistance, and (3) describes the recommended treatments for the reaction. Therefore, your petition does not seek to add new information to ACEI labeling. Instead, your petition seeks to place the angioedema warning into a box.

[1] West, Diane, "Cardio Drugs Live Off Fat of the Land," *Drug Store News* 17 (Feb. 18, 2002)(reporting that 101 million prescriptions for ACE inhibitors were filled in 2001); "Biovail Acquires Vasotec from Merck and Co., Inc.," *CCN Newswire* (May 12, 2002) (reporting that ACE inhibitors, including combinations with hydrochlorothiazide, had "prescription volumes of nearly 114 million" in 2001).

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II. ANALYSIS

FDA may, in its discretion, require drug products to bear a boxed warning (commonly referred to as a *Black Box warning*) to emphasize special problems, particularly those associated with death or serious injury (21 CFR 201.57(e)). However, we exercise this discretion judiciously to preserve the impact and significance of boxed warnings. With regard to the risk of severe angioedema, we believe that the rare adverse reaction is already adequately addressed in ACEI labeling.

A. Current ACEI Labeling Fully Informs Physicians of the Rare, but Serious, Risk of Life-threatening Angioedema

FDA recognizes that severe angioedema may be associated with ACEI treatment, but available data suggest that it is a rare occurrence. In particular, medical literature[2] and data from the Adverse Event Reporting System (AERS) support this conclusion. According to AERS, ACEI-associated angioedema has resulted in 141 reported deaths and 2,100 reported incidents of hospitalization.[3] Considering that over 100 million ACEI prescriptions were filled in the year 2001 alone, the number of reported incidents of life-threatening angioedema suggests a low rate of occurrence.

Nevertheless, current ACEI labeling includes extensive discussion of the potential reaction in the *Indications and Usage, Contraindications, Warnings, Precautions,* and *Adverse Reactions* sections. Although the content varies from product to product, ACEI labeling (1) warns of the risk of angioedema; (2) describes the signs and symptoms that angioedema patients commonly present; and (3) provides recommended treatments (e.g., epinephrine, discontinuation of drug treatment). The following, for example, is an excerpt from an ACE inhibitor's current labeling:

> **INDICATIONS AND USAGE . . .**
> In considering use of VASOTEC, it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, *Angioedema.*)
>
> **CONTRAINDICATIONS**
> VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

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[2] *See, e.g.,* Slater E, et al., "Clinical Profile of Angioedema Associated With Angiotensin Converting-Enzyme Inhibition," *JAMA* 260:967 (Aug. 19, 1988); Vleeming W, et al., "Ace Inhibitor-Induced Angioedema: Incidence, Prevention and Management," *Drug Safety* 18(3):171 (Mar. 1998).

[3] These figures are current as of September 2002. They may include duplicate reports of the same incident and/or reports that were incorrectly attributed. Therefore, the actual number of reported incidents may be lower.

WARNINGS . . .
Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including VASOTEC. This may occur at any time during treatment. In such cases VASOTEC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)
Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

PRECAUTIONS . . . *Information for Patients*
Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

ADVERSE REACTIONS . . .
Angioedema: Angioedema has been reported in patients receiving VASOTEC, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

In sum, ACEI labeling fully informs physicians about angioedema including (1) the nature of the risk, (2) the symptoms, (3) the treatments, and (4) the information that should be told to patients about the reaction.

B. A Boxed Warning Likely Would Not Reduce the Incidence of Angioedema

The nature of angioedema suggests that a boxed warning is unlikely to reduce the incidence of the reaction. As you acknowledge in your petition, its occurrence is generally unpredictable. While some populations are at an increased risk, no population is at an extreme risk.[4] While approximately one-third of the incidents occur within the first day of exposure, the remaining two-thirds occur over the first few months of ACEI use. Because of this lack of predictability, the reaction is generally not preventable. Therefore, boxing the angioedema warning is unlikely to reduce its incidence. Because the reaction is generally not preventable, the current ACEI labeling focuses on educating physicians and patients regarding the risk of angioedema, including (1) informing

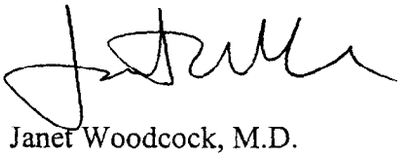
[4] The obvious exception is patients with a history of ACEI-associated angioedema, but ACE inhibitors are contraindicated for that population.

patients to seek medical assistance promptly if symptoms develop, and (2) giving physicians recommendations on how to treat patients when the reaction occurs.

III. CONCLUSION

Life-threatening angioedema rarely occurs in association with ACEI treatment. The extensive discussion of angioedema in the current labeling of ACE inhibitors educates physicians about the potential reaction and adequately protects the public health. Putting the angioedema warning into a box would be unlikely to reduce the incidence of the reaction. Therefore, we conclude that a boxed warning is not warranted. We will continue to monitor the incidence of severe ACEI-associated angioedema and, if appropriate, may take action in the future to ensure that physicians and patients continue to be adequately informed regarding the risk of this reaction (e.g., updating physician labeling, developing a patient package insert). For the reasons described above, your petition is denied.

Sincerely yours,



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