DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-221/S-027
19-309/S-025

Biovail Technologies Limited
Attention: Ms. Beth Ferguson
3725 Concorde Parkway
Chantilly, VA 20151

Dear Ms. Ferguson:

Please refer to your supplemental new drug applications dated August 3, 2000 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vaseretic® (enalapril maleate/hydrochlorothiazide) 10/25 mg Tablets (NDA 19-221/S-027) and Vasotec™ (enalaprilat) 1.25 mg/mL I.V. (NDA 19-309/S-025).

We acknowledge receipt of your submissions dated March 22, 2002 that constitute a complete response to our May 26, 2001 action letter.

These supplemental new drug applications provide for final printed labeling (FPL) revised as follows:

NDA 19-221/S-027

1. A new subsection entitled *Geriatric Use* has been added to the **PRECAUTIONS** section as follows:

   PRECAUTIONS:
   Geriatric Use

   Clinical studies of VASERETIC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

   This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of the hypertensive patient should always include assessment of renal function.
   (See **DOSAGE AND ADMINISTRATION**.)

2. Under **DOSAGE AND ADMINISTRATION,** the subsection *Use in the Elderly* has been deleted.

NDA 19-309/S-025

1. A new subsection entitled *Geriatric Use* has been added to the **PRECAUTIONS** section as follows:

PRECAUTIONS:
Geriatric Use

Clinical studies of VASOTEC I.V. did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of the hypertensive patient should always include assessment of renal function.
(See DOSAGE AND ADMINISTRATION.)

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the final printed labeling (package insert) submitted March 22, 2002. Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Alisea Sermon, Pharm.D.
Regulatory Project Manager
(301) 594-5334

Sincerely,

{See appended electronic signature page}

Douglas C.Throckmorton M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doug Throckmorton

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