DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-998/S-070
19-221/S-037

Biovail Technologies, Ltd.
Attention: Robert W. Ashworth, Ph.D.
700 Route 202/206 North
Bridgewater, NJ 08807

Dear Dr. Ashworth:

Please refer to your supplemental new drug applications dated May 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasotec® (enalapril maleate) 2.5, 5, 10 and 20 mg Tablets (NDA 18-998) and Vaseretic® (enalapril maleate/hydrochlorothiazide) 5/12.5 and 10/25 mg Tablets (NDA 19-221).

We also acknowledge receipt of your submissions dated October 25, 2007 for Vasotec® and Vaseretic®.

These Changes Being Effected supplements provide for revisions to the **WARNINGS/***Fetal/Neonatal Morbidity and Mortality* subsection and **PRECAUTIONS/***Pregnancy* subsection. These changes are based on a published article in the New England Journal of Medicine dated June 8, 2006, entitled, "*Major Congenital Malformations after First-trimester Exposure to ACE Inhibitors*". We also note the proposed labeling modifications to the **HOW SUPPLIED**/*Storage* subsections for Vasotec® and Vaseretic® based on ICH guidelines.

Also, as requested in the Agency's correspondence letter dated, January 9, 2003, class labeling updates have been made to the **WARNINGS**/*Angioedema* sections for Vasotec® and Vaseretic®.

Vasotec, NDA 18-998

1. Under the **CLINICAL PHARMACOLOGY/***Clinical Pharmacology in Pediatric Patients* subsection, the percentage of mean urinary recovery has been updated in accordance to our approval letter dated February 13, 2001.

   From:
   At steady state, the mean effective half-life for accumulation of enalaprilat was 14 hours and the mean urinary recovery of total enalapril and enalaprilat in 24 hours was 67% of the administered dose. Conversion of enalapril to enalaprilat was in the range of 64-76%.

   To:
   At steady state, the mean effective half-life for accumulation of enalaprilat was 14 hours and the mean urinary recovery of total enalapril and enalaprilat in 24 hours was 68% of

the administered dose. Conversion of enalapril to enalaprilat was in the range of 63-76%.

2. Under **WARNINGS**/*Angioedema* subsection, the "*Angioedema*" subsection heading has been revised to *Head and Neck Angioedema*.

3. Under **WARNINGS**, following the *Head and Neck Angioedema* subsection, the following paragraph has been added:

   Intestinal Angioedema*:* Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

4. Under **WARNINGS/** *Fetal/Neonatal Morbidity and Mortality* subsection**,** the following paragraph has been added.

   In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor during their first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated.

5. Under **PRECAUTIONS**/*Pregnancy* subsection, the following paragraph has been modified

   From:
   Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

   To:
   Female patients of childbearing age should be told about the consequences of exposure to ACE inhibitors. These patients should be asked to report pregnancies to their physicians as soon as possible.

6. Under **HOW SUPPLIED**/*Storage* subsection, the following text has been changed

   From:
   Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F). Keep container tightly closed. Protect from moisture. Dispense in a tight container as per USP, if product package is subdivided.

   To:
   Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from moisture. Dispense in a tight container as per USP, if product package is subdivided.

Additionally, the following editorial changes were noted:

- Correction of bolding or italics when referencing sections or subsections.
- Under **HOW SUPPLIED**, the text "unit of" has been omitted from the bottle description for the following NDC's:
  64455-141-30
  64455-142-30
  64455-143-30
- The revised date has been updated under the **HOW SUPPLIED** section.

Vaseretic, NDA 19-221

1. Under **WARNINGS**/*Angioedema* subsection, the "*Angioedema*" heading has been revised to *Head and Neck Angioedema*.

2. Under **WARNINGS**, following the *Head and Neck Angioedema* subsection, the following paragraph has been added:

   Intestinal Angioedema*:* Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

3. Under **WARNINGS/** *Fetal/Neonatal Morbidity and Mortality* subsection, the following paragraph has been added.

   In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor during their first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated.

4. Under **PRECAUTIONS/***Pregnancy* subsection, the following paragraph has been modified

   From:
   Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

   To:
   Female patients of childbearing age should be told about the consequences of exposure to ACE inhibitors. These patients should be asked to report pregnancies to their physicians as soon as possible.

5. Under **HOW SUPPLIED/***Storage* subsection, the following text has been changed

   From:
   Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F). Keep container tightly closed. Protect from moisture.
   Dispense in a tight container as per USP, if product package is subdivided.

   To:
   Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from moisture. Dispense in a tight container as per USP, if product package is subdivided.

Additionally, the following editorial changes were noted:

- Correction of bolding or italics when referencing sections or subsections.
- The revised date has been updated under the **HOW SUPPLIED** section.

We have completed our review of these applications and they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. The final printed labeling (FPL) must be identical to the electronic draft labeling package inserts.

Within 14 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the submitted electronic draft labeling text dated October 25, 2007. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "SPL for approved supplements NDA 18-998/S-070 and NDA 19-221/S-037."Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Alisea Crowley, Pharm.D.
Regulatory Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc: SRL Keller and Heckman
Attention: Mr. John Dubeck
US Agent c/o Biovail Laboratories International
1001 G Street, NW, Suite 500 West
Washington, DC 20001

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/s/

Norman Stockbridge

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