DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-998/S-071
19-221/S-038

Biovail Laboratories International SRL
Attention: Robert W. Ashworth, Ph.D.
Chelston Park, Building 2
Collymore Rock
St. Michael, BHI
Barbados, West Indies

Dear Dr. Ashworth:

Please refer to your supplemental new drug applications dated April 4, 2008 (NDA 18-998/S-071) and April 11, 2008 (NDA 19-221/S-038) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate) 2.5, 5, 10 and 20 mg and Vaseretic (enalapril maleate/hydrochlorothiazide) 5/12.5 and 10/25 mg Tablets respectively.

We also acknowledge receipt of your submissions dated August 28, 2008.

These Changes Being Effected supplemental applications provide for additional information in the **PRECAUTIONS/Drug Interactions** section of the package insert as requested in our letter dated March 3, 3008.

These supplemental new drug applications provide for electronic draft labeling with the following revisions:

18-998/S-071

1. Under the **DESCRIPTION** section, "and other ingredients" in the inactive ingredients list has been deleted and replaced with sodium bicarbonate.

2. Under the **PRECAUTIONS/*Drug Interactions*** subsection, the following interaction has been added:

   Gold:
   Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including VASOTEC.

19-221/S-038

3. Under the **DESCRIPTION** section, "and other ingredients" in the inactive ingredients list has been deleted and replaced with sodium bicarbonate.

4. Under the **PRECAUTIONS/*Drug Interactions*** subsection, the following interaction has been added:

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE Inhibitor therapy including VASERETIC.

5. We also note the following revisions to the package insert to reflect removing reference to the 5-12.5 mg tablet as it is being discontinued. The removal of the 5-12.5 mg strength is reflected in the **DESCRIPTION**, **INDICATIONS AND USAGE**, **DOSAGE AND ADMINISTRATION**, and **HOW SUPPLIED** sections of the package insert.

    - Under the **DESCRIPTION** section, the following sentence has been changed to read as follows:

      VASERETIC is available in the tablet combination of enalapril maleate with hydrochlorothiazide: VASERETIC 10-25, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide.

    - Under the **INDICATIONS AND USAGE** section, the second sentence has been changed to read as follows:

      This fixed dose combination is not indicated for initial treatment (see **DOSAGE AND ADMINISTRATION**).

    - Under the **DOSAGE AND ADMINISTRATION**/*Dose Titration Guided by Clinical Effec*t subsection, reference to VASERETIC 5-12.5 has been removed and this subsection reads as follows:

      Dose Titration Guided by Clinical Effect: A patient whose blood pressure is not adequately controlled with either enalapril or hydrochlorothiazide monotherapy may be given VASERETIC 10-25. Further increases of enalapril, hydrochlorothiazide or both depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have elapsed. In general, patients do not require doses in excess of 20 mg of enalapril or 50 mg of hydrochlorothiazide. The daily dosage should not exceed two tablets of VASERETIC 10-25.

    - Under the **HOW SUPPLIED** section, the following text has been deleted:

      VASERETIC Tablets 5-12.5 mg, are green, squared capsule-shaped compressed tablets, coded MSD on one side and 173 on the other. Each tablet contains 5 mg of enalapril maleate and 12.5 mg of hydrochlorothiazide. They are supplied as follows: NDC 64455-145-01 bottles of 100 (with desiccant).

We also note the last revised labeling date has been updated to March 2008 for both Vasotec and Vaseretic.

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 electronic draft labeling text. 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 labeling dated August 28, 2008. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

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.
Senior Regulatory Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
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Center for Drug Evaluation and Research

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/s/

Norman Stockbridge

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