DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020528/S-018

SUPPLEMENT APPROVAL

Abbott Laboratories
Attention: Viraj B. Gandhi
Manager, U.S. and Canada Regulatory Affairs
200 Abbott Park Road
Dept. PA77/ Bldg. AP30-LL
Abbott Park, IL 60064-6157

Dear Mr. Gandhi:

Please refer to your Supplemental New Drug Application (sNDA) dated July 13, 2011, received July 14, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mavik (trandolapril) 1 mg, 2 mg, and 4 mg Tablets.

We acknowledge receipt of your amendment dated January 13, 2012.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows:

1. Under **INDICATIONS AND USAGE**, the following text was deleted:

   > In considering the use of MAVIK, it should be noted that in controlled trials ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients.

2. Under **CONTRAINDICATIONS,** the words "in patients with hereditary/idiopathic angioedema" were added to the first paragraph. The paragraph now reads:

   > MAVIK is contraindicated in patients who are hypersensitive to this product, in patients with hereditary/idiopathic angioedema and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

3. Under **WARNINGS, Head and Neck Angioedema**, the first paragraph was changed from:

In considering the use of MAVIK, it should be noted that in controlled trials ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients.

To:

In controlled trials ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients

4. Under **PRECAUTIONS, Drug Interactions,** a new section was added:

   Antidiabetic Agents

   Concomitant use of ACE inhibitors and antidiabetic medicines (insulin or oral hypoglycemic agents) may cause an increased blood glucose lowering effect with greater risk of hypoglycemia.

5. Under **ADVERSE REACTIONS, Cardiovascular**, the following text was deleted from the list:

   hypotension

6. Under **ADVERSE REACTIONS, Metabolism and Endocrine,** the following was deleted:

   Increased creatinine, increased potassium

7. Under **ADVERSE REACTIONS**, a new section was added:

   Postmarketing

   The following adverse reactions were identified during post approval use of MAVIK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

   General Body Function
   Malaise, fever.

   Cardiovascular
   Myocardial infarction, myocardial ischemia, angina pectoris, cardiac failure, ventricular tachycardia, tachycardia, transient ischemic attack, arrhythmia.

Central Nervous System
Cerebral hemorrhage.

Dermatologic
Alopecia, sweating, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Emotional, Mental, Sexual States
Hallucination, depression.

Gastrointestinal
Dry mouth, pancreatitis, jaundice and hepatitis.

Hemopoietic
Agranulocytosis, pancytopenia.

Metabolism and Endocrine
Increased SGOT (AST).

Pulmonary
Bronchitis.

Renal and Urinary
Renal failure.

8. Under **ADVERSE REACIONS, Clinical Laboratory Test Findings, *Hematology***, the following text was deleted:

   (See **WARNINGS**). Low white blood cells, low neutrophils, low lymphocytes,

9. Under **ADVERSE REACIONS, Clinical Laboratory Test Findings, *Serum Electrolytes,*** the following text was deleted:

   Hyperkalemia (see **Precautions**)

10. Under **OVERDOSAGE**, the sentence "Symptoms also expected with ACE inhibitors are hypotension, hyperkalemia, and renal failure" was added as the last sentence to the first paragraph. The paragraph now reads:

    No data are available with respect to overdosage in humans. The oral LD50 of trandolapril in mice was 4875 mg/Kg in males and 3990 mg/Kg in females. In rats, an oral dose of 5000 mg/Kg caused low mortality (1 male out of 5; 0 females). In dogs, an oral dose of 1000 mg/Kg did not cause mortality and abnormal clinical signs were not observed. In humans, the most likely clinical manifestation would be symptoms attributable to severe hypotension. Symptoms also expected with ACE inhibitors hypotension, hyperkalemia, and renal failure.

We have completed our review of this supplemental application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of

promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MARY R SOUTHWORTH
01/23/2012