DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 017963/S-063
NDA 018704/S-023

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Donna Vivelo
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Vivelo:

Please refer to your supplemental new drug applications dated June 29, 2009, received June 29, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lopressor (metoprolol tartrate) 50 mg, 100 mg Tablets and 5 mg/5 mL Ampules for Injection.

These "Changes Being Effected" supplemental new drug applications provide for revisions to the **CONTRAINDICATIONS, WARNINGS,** and **DOSAGE AND AMINISTRATION s**ections of the label. The following changes were made:

1. In **CONTRAINDICATIONS**, "Pheochromocytoma (see **WARNINGS**)", has been removed.

2. In **WARNINGS**, a box as been placed around the paragraph regarding Ischemic Heart Disease.

3. In **WARNINGS/*Pheochromocytoma***, the paragraph has been changed from:

   In patients known to have, or suspected of having, a pheochromocytoma, Lopressor is contraindicated (see **CONTRAINDICATIONS**). If Lopressor is required, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta mediated vasodilatation in skeletal muscle.

   To:

   If Lopressor is used in the setting pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

4. In **DOSAGE AND ADMINISTRATION/Hypertension**, the word "tablets" has been added in several places, the paragraph now reads:

   The dosage of Lopressor tablets should be individualized. Lopressor tablets should be taken with or immediately following meals.

   The usual initial dosage of Lopressor tablets is 100 mg daily in single or divided doses, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. The effective dosage range of Lopressor tablets is 100-450 mg per day. Dosages above 450 mg per day have not been studied. While once-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period, and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. $Beta_1$ selectivity diminishes as the dose of Lopressor is increased.

5. In **DOSAGE AND ADMINISTRATION/Angina Pectoris,** the word "tablets" has been added in several places, the paragraph now reads:

   The dosage of Lopressor tablets should be individualized. Lopressor tablets should be taken with or immediately following meals.

   The usual initial dosage of Lopressor tablets is 100 mg daily, given in two divided doses. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is pronounced slowing of the heart rate. The effective dosage range of Lopressor tablets is 100-400 mg per day. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks (see WARNINGS).

6. The revision date and version number have been updated.

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 enclosed, agreed upon labeling text, which is identical to the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format submitted on June 26, 2009.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

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
(301) 796 3975

Sincerely,

{See appended electronic signature page}

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

Enclosure: Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-17963	SUPPL-63	NOVARTIS PHARMACEUTICALS CORP	LOPRESSOR(METOPROLOL TARTRATE) TABLETS
NDA-18704	SUPPL-23	NOVARTIS PHARMACEUTICALS CORP	LOPRESSOR (METOPROLOL TARTRATE) INJECTIN

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
11/20/2009