DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-303/S-025

Novartis Pharmaceuticals Corporation
Attention: Ms. Donna M. Vivelo
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Ms. Vivelo:

Please refer to your supplemental new drug application dated March 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lopressor HCT (metoprolol tartrate and hydrochlorothiazide) 50/25, 100/25 and 100/50 Tablets.

We acknowledge receipt of your submissions dated March 17 and August 14, 2003. Your submission of August 14, 2003 constituted a complete response to our February 28, 2003 action letter.

This supplemental new drug application provides for electronic final printed labeling (FPL) revised as follows:

1. The following subsection has been added to the end of the **PRECAUTIONS** section:

   Geriatric Use

   Clinical studies of Lopressor HCT 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. Hydrochlorothiazide 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, and it may be useful to monitor renal function. (See WARNINGS). 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 concomitant disease or other drug therapy.

2. The chemical name has been changed to be consistent with the current USP name from:

   (+)-1-Isopropylamino-3-[p-(2-methoxyethyl)phenoxy]-2-propanol 2:1 dextro-tartrate salt.

   To:

   (+)-1-(Isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) salt.

In addition, the following changes were noted in the labeling:

1. Under the **HOW SUPPLIED** section, the following changes have been made in the description of the tablets:

   a. The phrase, “white and blue” changed to, “white and mottled-blue” for 50/25 mg tablets
   b. The phrase, “white and pink” changed to, “white and mottled-pink” for 100/25 mg tablets

c. The phrase, “white and yellow” changed to, “white and mottled-yellow” for 100/50 mg tablets

We have completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the electronic final printed labeling submitted on August 14, 2003.

At the time of the next printing, please make the following changes:

1. Add the following to the end of the **CLINICAL PHARMACOLOCGY/Pharmacokinetics** section:

   In elderly subjects with clinically normal renal and hepatic function, there are no significant differences in metoprolol pharmacokinetics compared to young subjects.

2. Change the storage statement on the package insert, immediate container and carton label to read:

   Store at 25˚C (77˚F); excursions permitted to 15-30˚C (59-86˚F)
   [see USP Controlled Room Temperature]

   Or, if space on the immediate container or the carton is limited, the use of an abbreviated statement could be used in accordance with the FDA stability guidance provisions, such as:

   Store at 25˚C (77˚F) [see insert]

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, 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:

Ms. Melissa Robb
Regulatory Project Manager
(301) 594-5313

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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