DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-704/S-015
NDA 17-963/S-058

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 applications dated March 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lopressor (metoprolol tartrate) 5mg/mL Injection (NDA 18-704/S-015) and Lopressor (metoprolol tartrate) 50 and 100mg Tablets (NDA 17-963/S-058).

We acknowledge receipt of your submissions dated January 20, 2003 and March 11, 2003. Your submissions of March 11, 2003 constituted a complete response to our January 9, 2003 action letter.

These supplemental new drug applications provide for final printed labeling (FPL) revised as follows:

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

   Geriatric Use

   Clinical trials of Lopressor in hypertension did not include sufficient numbers of elderly patients to determine whether patients over 65 years of age differ from younger subjects in their response to Lopressor. Other reported clinical experience in elderly hypertensive patients has not identified any difference in response from younger patients.

   In worldwide clinical trials of Lopressor in myocardial infarction, where approximately 478 patients were over 65 years of age (0 over 75 years of age), no age-related differences in safety and effectiveness were found. Other reported clinical experience in myocardial infarction has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some elderly individuals taking Lopressor cannot be categorically ruled out. Therefore, in general, it is recommended that dosing proceed with caution in this population.

The following changes were noted in both NDAs:

1. In the **DESCRIPTION** SECTION, the term "USP" has been added after "metoprolol tartrate" in the first sentence of the first paragraph.

2. In the **DESCRIPTION** section, the phrase "and water for injection USP" has been added to the end of the second sentence of the first paragraph.

3. In the **HOW SUPPLIED** section, the reference to the Unit Dose (blister pack) Box of 100 (strips of 10) has been deleted for both the 50 mg and 100 mg tablets.

The following changes were noted in NDA 18-704/S-015:

1. Under the **DESCRIPTION** section, "(±)-" has been inserted after "Metoprolol tartrate is" in the third sentence in the first paragraph.

2. Under the **PRECAUTIONS/ Drug Interactions** section, the following title has been added to the second paragraph:

   Risk of Anaphylactic Reaction.

3. The following has been added to the end of the **ADVERSE REACTIONS/Hypertension and Angina**/*Gastrointestinal* subsection:

   Post-marketing experience reveals very rare reports of hepatitis, jaundice and non-specific hepatic dysfunction. Isolated cases of transaminase, alkaline phosphatase, and lactic dehydrogenase elevations have also been reported.

4. The following have been deleted from the **HOW SUPPLIED** section, Tablets 50 mg subsection:

   Gy-Pak-One Unit

   12 bottles-60 tablets each……..NDC 0028-0051-73
   12 bottles-100 tablets each……NDC 0028-0051-65

5. The following have been deleted from the **HOW SUPPLIED** section, Tablets 100 mg subsection:

   Gy-Pak-One Unit

   12 bottles- 60 tablets each……NDC 0028-0071-73
   12 bottles- 100 tablets each……..NDC 0028-0071-65

6. The following changes have been made to the **HOW SUPPLIED** section, following the description of both 50 mg and 100 mg tablets:

   Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.
   Store between 59°-86° F (15°-30° C). Protect from moisture.
   Dispense in tight, light-resistant container (USP).

   To:

   Store between 15°C-30°C (59°F-86°F). Protect from moisture.
   Dispense in tight, light-resistant container (USP).

7. The following changes have been made to the **HOW SUPPLIED** section, following the description of the 5 mL ampuls:

   ()()----------

   To:

   Do not store above 30°C (86°F). Protect from light.

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 final printed labeling submitted on March 11, 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, then the use of an acceptable abbreviated statement could be used in accord 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/

Norman Stockbridge
9/12/03 11:59:43 AM
For Douglas Throckmorton