DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-386/S-039

Baxter Healthcare Corporation
Attention: Ivy Bautista
Director, Regulatory Affairs
95 Spring Street
New Providence, NJ 07974

Dear Ms. Bautista:

Please refer to your supplemental new drug application (NDA) dated April 24, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brevibloc (esmolol hydrochloride) 10 mg/mL, 20 mg/mL and 250 mg/mL IV.

We also refer to your amendment dated September 17, 2007.

This supplemental new drug application provides for the following label revisions in the package insert to reflect the discontinuation of the 250 mg/mL ampul concentrate dosage form.

1) To delete the following text from the beginning of the package insert just prior to the **DESCRIPTION** section of the labeling:

> **"BREVIBLOC CONCENTRATE**
>
> (Esmolol Hydrochloride)
>
> **2,500 mg/10 mL (250 mg/mL)** Ampuls for Dilution
>
> 10 mL Ampuls
>
> **NOT FOR DIRECT INTRAVENOUS INJECTION.**
>
> Esmolol Hydrochloride concentration = 250 milligrams/mL (250,000 micrograms/mL)
>
> **AMPULS MUST BE DILUTED PRIOR TO INFUSION - SEE DOSAGE AND ADMINISTRATION, Directions for Use of the Brevibloc Concentrate 10 mL Ampul (250 milligrams/mL)."**

2) To delete the following text that comprises the last paragraph in the **DESCRIPTION** section of the labeling:

"Brevibloc Concentrate

BREVIBLOC CONCENTRATE is a clear, colorless to light yellow, sterile, nonpyrogenic concentrate.

2500 mg, 10 mL Ampul – Each mL contains 250 mg Esmolol Hydrochloride in 25% Propylene Glycol, USP, 25% Alcohol, USP and Water for Injection, USP; buffered with 17.0 mg Sodium Acetate Trihydrate, USP, and 0.00715 mL Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary, to adjust pH to 3.5-5.5. NOT FOR DIRECT INTRAVENOUS USE - AMPUL MUST BE DILUTED PRIOR TO INFUSION. See **DOSAGE AND ADMINISTRATION**, **Directions for Use of the Brevibloc Concentrate 10 mL Ampul (250 milligrams/mL)**."

3) To delete the following paragraphs from the **PRECAUTIONS** section, **General** subsection of the labeling:

"Infusion concentrations of 20 mg/mL were associated with more serious venous irritation, including thrombophlebitis, than concentrations of 10 mg/mL with BREVIBLOC CONCENTRATE, extravasation of 20 mg/mL or higher may lead to a serious local reaction and possible skin necrosis. Concentrations greater than 10 mg/mL or infusion into small veins or through a butterfly catheter should be avoided."

and

"Care should be taken in the intravenous administration of BREVIBLOC CONCENTRATE as sloughing of the skin and necrosis have been reported in association with infiltration and extravasation of intravenous infusions."

4) To delete the following text from the **DOSAGE AND ADMINISTRATION** section of the labeling:

"Directions for Use of the Brevibloc Concentrate 10 mL Ampul (250 milligrams/mL)

THE 2500 mg AMPUL IS NOT FOR DIRECT INTRAVENOUS INJECTION. THIS DOSAGE FORM IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED PRIOR TO ITS INFUSION. BREVIBLOC SHOULD NOT BE ADMIXED WITH SODIUM BICARBONATE. BREVIBLOC SHOULD NOT BE MIXED WITH OTHER DRUGS PRIOR TO DILUTION IN A SUITABLE INTRAVENOUS FLUID. (See Compatibility Section below.)

Dilution: Aseptically prepare a 10 mg/mL infusion by adding two 2500 mg ampuls to a 500 mL container or one 2500 mg ampul to a 250 mL container of a compatible intravenous solution listed below. (Remove overage prior to dilution as appropriate.) This yields a final concentration of 10 mg/mL. The diluted solution is stable for at least 24 hours at room temperature. Note: The use of esmolol with propylene glycol has been

associated with a higher incidence of venous irritation at concentrations greater than 10 mg/mL on continued infusion. Mixed from the ampul at concentrations of greater than 10 mg/mL BREVIBLOC has, however, been well tolerated when administered *via* a central vein."

5) To delete the following text from the **HOW SUPPLIED** section of the labeling:

"BREVIBLOC CONCENTRATE

NDC 10019-025-18, 2500 mg – 10 mL Ampuls for Dilution, Package of 10"

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed electronic labeling text. We will transmit the SPL version of the labeling submitted on September 17, 2007 to the National Library of Medicine for public dissemination.

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

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 Dan Brum, Pharm.D., MBA, Regulatory Health Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal 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

11/6/2007 05:54:58 PM