DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-386/S-022

Baxter Healthcare Corporation, Anesthesia & Critical Care
Attention: Ms. Lidia Mostovy
95 Spring Street
New Providence, NJ 07974

Dear Ms. Mostovy:

Please refer to your supplemental new drug application dated January 28, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brevibloc Double Strength Injection (esmolol hydrochloride) 20 mg/mL in 5 mL ready-to-use vials.

This supplemental new drug application provides for the marketing of a new double strength formulation in 5 mL vials. This formulation was approved for marketing in 100 mL bags on January 27, 2003 with the approval of S-020.

This supplement proposes the following changes to the package insert:

1. The following changes were made in the title under the **BREVIBLOC PREMIXED** INJECTION:

    a. (Esmolol Hydrochloride) changed to (Esmolol Hydrochloride in Sodium Chloride)

    b. The addition of the following on the next line: 2,500 mg/250 mL (10mg/mL)

    c. Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride changed to Iso-Osmotic Solution of Esmolol Hydrochloride

2. The following changes were made in the title under **BREVIBLOC PREMIXED** INJECTION **DOUBLE STRENGTH**:

    a. The title was changed from **BREVIBLOC PREMIXED** INJECTION to **BREVIBLOC DOUBLE STRENGTH PREMIXED** INJECTION

    b. (Esmolol Hydrochloride) **DOUBLE STRENGTH** changed to (Esmolol Hydrochloride in Sodium Chloride)

    c. The addition of the following on the next line: 2,000mg/100mL (20mg/mL)

    d. Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride changed to Iso-Osmotic Solution of Esmolol Hydrochloride

3. The following changes were made in the title under **BREVIBLOC** INJECTION:

    a. (Esmolol Hydrochloride) changed to (Esmolol Hydrochloride in Sodium Chloride)

    b. The addition of the following on the next line: 100 mg/10 mL (10mg/mL)

    c. Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride changed to Iso-Osmotic Solution of Esmolol Hydrochloride

4. The addition of the following to the title:

   BREVIBLOC DOUBLE STRENGTH INJECTION
   (Esmolol Hydrochloride in Sodium Chloride)
   100 mg/5 mL (20 mg/mL)
   Ready-to-use Vials
   5 mL Vials
   Iso-Osmotic Solution of Esmolol Hydrochloride
   For Intravenous Use
   Can be used for direct intravenous use.
   Esmolol Hydrochloride concentration = 20 milligrams/mL (20,000 micrograms/mL)
   Single Patient Use Only
   No Preservatives Added

5. The following changes were made to the title under **BREVIBLOC** C0NCENTRATE:

   a. The addition of the following line: 2,500 mg/10 mL (250 mg/mL)

6. The following paragraph was added at the end of the **Brevibloc Injection** subsection of the **DESCRIPTION** section:

   100 mg, 5 mL DOUBLE STRENGTH Single Dose Vial – Each mL contains 20 mg Esmolol Hydrochloride, 4.1 mg Sodium Chloride, USP and Water for Injection, USP; buffered with 2.8 mg Sodium Acetate Trihydrate, USP and 0.546 mg Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary to adjust pH to 5.0 (4.5-5.5).

7. The second sentence in the **PRECAUTIONS**/**General** subsection was changed from:

   Extravasation of 20mg/mL may lead to a serious local reaction and possible skin necrosis.

   To:

   With BREVIBLOC CONCENTRATE, extravasation of 20mg/mL or higher may lead to a serious local reaction and possible skin necrosis.

8. The third paragraph in the **PRECAUTIONS/General** subsection was changed from:

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

   To:

   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.

9. The following sentence was added as the third sentence of the first paragraph of the **OVERDOSAGE/Acute Toxicity** subsection:

   Use of BREVIBLOC PREMIXED INJECTION and BREVIBLOC **DOUBLE STRENGTH** PREMIXED INJECTION may reduce the potential for dilution errors.

10. In the **DOSAGE AND ADMINISTRATION** section, the subsection title has been changed from:

    Directions for Use of Brevibloc Premixed Injection and Brevibloc Premixed Injection DOUBLE STRENGTH

To:

Directions for Use of Brevibloc Premixed Injection (10 mg/mL) and Brevibloc DOUBLE STRENGTH Premixed Injection (20 mg/mL)

11. The paragraph in the **DOSAGE AND ADMINISTRATION/Directions for Use of Brevibloc Premixed Injection (10 mg/mL) and Brevibloc DOUBLE STRENGTH Premixed Injection (20 mg/mL)** subsection has been changed from:

    This dosage from is prediluted to 100 or 250 mL to provide a ready-to-use, iso-osmotic solution of 20 or 10 mg/mL esmolol hydrochloride in sodium chloride. Do not introduce additives to BREVIBLOC PREMIXED INJECTION or BREVIBLOC PREMIXED INJECTION DOUBLE STRENGTH. See **Directions for Use of the Premixed Bag** for additional information.

    To:

    This dosage from is prediluted to 100 or 250 mL to provide a ready-to-use, iso-osmotic solution of either 20 or 10 mg/mL esmolol hydrochloride in sodium chloride. It is important not to introduce additives to BREVIBLOC PREMIXED INJECTION or BREVIBLOC **DOUBLE STRENGTH** PREMIXED INJECTION. See **Directions for Use of the Premixed Bag** for additional information.

12. The first three sentences of the first paragraph in the **DOSAGE AND ADMINISTRATION/Directions for Use of the Premixed Bag** subsection have been changed from:

    BREVIBLOC PREMIXED INJECTION and BREVIBLOC PREMIXED INJECTION – DOUBLE STRENGTH are provided in 250 mL and 100 mL IntraVia bags, which are ready-to-use, non-latex, non-PVC bags with two PVC ports, a medication port and a delivery port**. In the case of BREVIBLOC PREMIXED INJECTION, the medication port is to be used only for withdrawing an initial bolus from the bag; the medication withdrawal port is not intended for repeat bolus administration. Use aseptic technique when withdrawing the bolus dose.**

    To:

    Brevibloc Premixed Injection (10 mg/mL) 250 mL IntraVia Bag
    Brevibloc DOUBLE STRENGTH Premixed Injection (20 mg/mL) 100 mL IntraVia Bag
    BREVIBLOC PREMIXED INJECTION (10 mg/mL) and BREVIBLOC **DOUBLE STRENGTH** PREMIXED INJECTION (20 mg/mL) are provided in ready-to-use, non-latex, non-PVC bags with two PVC ports, a medication port and a delivery port. **The medication port is to be used solely for withdrawing an initial bolus from the bag; the medication withdrawal port is not intended for repeat bolus administration. The sterility of the premixed bag cannot be assured after repeat withdrawals from the bag. The use of aseptic technique is required when withdrawing the bolus dose.**

13. The following change was made to the first sentence of the last paragraph of the **DOSAGE AND ADMINISTRATION/Directions for Use of the Premixed Bag** subsection:

    The Brevibloc Premixed Injection DOUBLE STRENGTH contains Esmolol Hydrochloride at a concentration of 20 milligrams/mL.

    To:

    The Brevibloc **DOUBLE STRENGTH** Premixed Injection contains Esmolol Hydrochloride at a concentration of 20 milligrams/mL.

14. In the **DOSAGE AND ADMINISTRATION/Directions for Use of the Premixed Bag** subsection, the last sentence under the directions TO OPEN has been changed from:

Do not introduce additives to BREVIBLOC PREMIXED INJECTION or BREVIBLOC PREMIXED INJECTION – DOUBLE STRENGTH.

To:

Do not introduce additives to BREVIBLOC PREMIXED INJECTION or BREVIBLOC **DOUBLE STRENGTH** PREMIXED INJECTION.

15. In the **DOSAGE AND ADMINISTRATION** section, the subsection title has been changed from:

Directions for Use of the 10 mL Ready-to-use Vial (10 milligrams/mL)

To:

Directions for Use of the Ready-to-use Vials
Brevibloc Injection (10 mg/mL) 10 mL Ready-to-Use Vial
Brevibloc DOUBLE STRENGTH Injection (20 mg/mL) 5 mL Ready-to-use Vial

16. The first sentence in the **DOSAGE AND ADMINISTRATION/Directions for Use of the Ready-to-use Vial** subsection has been changed from:

This dosage form is prediluted to provide a ready-to-use, iso-osmotic solution of 10mg/mL esmolol hydrochloride in sodium chloride recommended for BREVIBLOC intravenous administration.

To:

This dosage form is prediluted to provide a ready-to-use, iso-osmotic solution of either 10 or 20 mg/mL esmolol hydrochloride in sodium chloride recommended for BREVIBLOC intravenous administration.

17. The following paragraph was added at the end of the **DOSAGE AND ADMINISTRATION/Directions for Use of the Ready-to-use Vial** subsection:

The 5 mL **DOUBLE STRENGTH** Ready-to-use Vial contains Esmolol Hydrochloride at a concentration of 20 milligrams/mL. When using a 20 milligrams/mL concentration, a loading dose of 0.5 mg/kg infused over 1 minute period of time, for a 70 kg patient is 1.75 mL.

18. The last two sentences of the **DOSAGE AND ADMINISTRATION/Directions for Use of the Brevibloc Concentrate 10 mL Ampul (250 milligrams/mL)** subsection has been changed from:

Concentrations of BREVIBLOC (Esmolol Hydrochloride) greater than 10 mg/mL are likely to produce irritation on continued infusion (see **PRECAUTIONS**). BREVIBLOC has, however, been well tolerated when administered via a central line.

To:

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 line.

19. The description of the BREVIBLOC INJECTION – DOUBLE STRENGTH in the **HOW SUPPLIED** section has been changed from:

BREVIBLOC PREMIXED INJECTION – DOUBLE STRENGTH

To:

BREVIBLOC **DOUBLE STRENGTH** PREMIXED INJECTION

20. The following has been added to the **HOW SUPPLIED** section:

BREVIBLOC **DOUBLE STRENGTH** INJECTION
NDC 10019-085-01, 5 Ml Ready-to-use Vials, Package of 10

Baxter Healthcare Corporation, Anesthesia & Critical Care proposes the container labels to have printing in seafoam green as was approved for the DOUBLE STRENGTH formulation in S-020 in 100 mL plastic bags. In the submission, there are proposed labels for the both the vial and the vial cartons.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

1. In the title under the **BREVIBLOC PREMIXED** INJECTION, **BREVIBLOC PREMIXED** INJECTION **DOUBLE STRENGTH, BREVIBLOC** INJECTION and **BREVIBLOC DOUBLE STRENGTH** INJECTION sections, the established name should remain "(Esmolol Hydrochloride)".

2. In the title under the **BREVIBLOC PREMIXED** INJECTION, **BREVIBLOC PREMIXED** INJECTION **DOUBLE STRENGTH, BREVIBLOC** INJECTION and **BREVIBLOC DOUBLE STRENGTH** INJECTION sections, the description should remain "Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride".

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted labeling (package insert and immediate container and carton labels submitted January 28, 2003). These revisions are terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-386/S-022". Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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 reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health 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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