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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-386/S-021

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-386/S-021

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

Dear Ms. Jambhekar:

Please refer to your supplemental new drug application dated October 24, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brevibloc Injection (esmolol hydrochloride) 10 mg/mL in 10 mL ready to use vials.

We acknowledge receipt of your submission dated January 13, 2003.

This supplemental new drug application provides for a new isotonic formulation of Brevibloc Injection 10 mg/mL in 10 mL vials. This supplement also represents the completion of a phase 4 commitment which was agreed upon by Baxter Healthcare Corporation, Anesthesia & Critical Care with the approval of a supplemental application, S-018, for Brevibloc Premixed Injection 10mg/mL packaged in 250 mL Bags on February 16, 2001. The commitment was as follows:

> Baxter PPI makes a post-approval commitment to reevaluate the subject formulation to either eliminate or significantly reduce overage of esmolol HCl added in the formulation, and submit it as a supplement. The detailed plans of action will be submitted by August 2001 for the Brevibloc Premixed Injection and by February 2002 for the Brevibloc Concentrate. At the time you submit your plans, please include a date that the supplement(s) will be submitted.

This supplement proposes the following changes to the package insert:

1. The addition of the following to the title of the package insert:

   BREVIBLOC PREMIXED INJECTION
   (Esmolol Hydrochloride)
   DOUBLE STRENGTH
   Ready-to-use Bags
   100 mL Bags
   Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride
   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

2. The addition of the following line to the title under the **BREVIBLOC INJECTION**, Ready-to-use Vials, 10mL Vials:

   Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride

3. The addition of the following paragraph at the end of the **DESCRIPTION** section, **Brevibloc Premixed Injection** subsection:

2000 mg, 100 mL Single Use Premixed Bag DOUBLE STRENGTH – 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). The calculated osmolarity is 312 mOsmol/L. The 100 mL bag is non-latex, non-PVC IntraVia bag with dual PVC ports. The IntraVia bag is manufactured from a specially designed multilayer plastic (PL 2408). Solutions in contact with the plastic container leach out certain chemical compounds from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. See **DOSAGE AND ADMINISTRATION, Directions for Use of the Premixed Bag** for additional information.

4. The **DESCRIPTION/Brevibloc Injection** subsection has been changed from:

BREVIBLOC INJECTION is a clear, colorless to light yellow, sterile, nonpyrogenic solution.
100 mg, 10 mL Single Dose Vial – Each mL contains 10 mg Esmolol Hydrochloride 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 4.5-5.5.

To:

BREVIBLOC INJECTION is a clear, colorless to light yellow, sterile, nonpyrogenic, iso-osmotic solution of esmolol hydrochloride in sodium chloride.
100 mg, 10 mL Single Dose Vial – Each mL contains 10 mg Esmolol Hydrochloride, 5.9 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).

5. Under the **DOSAGE AND ADMINISTRATION** section, the subsection heading has been changed from:

Directions for Use of Brevibloc Premixed Injection

To:

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

6. Under the **DOSAGE AND ADMINISTRATION/Directions for Use of Brevibloc Premixed Injection and Brevibloc Premixed Injection DOUBLE STRENGTH** subsection, the paragraph has been changed from:

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

To:

This dosage form 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.

7. Under the **DOSAGE AND ADMINISTRATION/Directions for Use of the Premixed Bag** subsection, the first sentence has been changed from:

BREVIBLOC PREMIXED INJECTION is provided in 250 mL IntraVia bags, which are ready-to-use, non-latex, non-PVC bags with two ports, a medication port and a delivery port.

To:

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 ports, a medication port and a delivery port.

8. The following paragraph was added to the end 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. When using 20 milligrams/mL concentration, a loading dose of 0.5 milligrams/kg infused over 1 minute period of time, for a 70 kg patient, is 1.75 mL. The loading dose can be removed from the medication port of the premixed bag.

9. In Figure 1. Two-Port IntraVia Bag, the text to describe the two ports, "Medication Port (for withdrawing initial bolus)" and "Delivery Port", was deleted.

10. 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.

    To:

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

11. The first sentence under the **DOSAGE AND ADMINISTRATION/Directions for Use of the 10 mL Ready-to-use Vial (10 milligrams/mL)** subsection has been changed from:

    This dosage form is prediluted to provide a ready to use 10mg/mL concentration recommended for BREVIBLOC intravenous administration.

    To:

    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.

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

    BREVIBLOC PREMIXED INJECTION – DOUBLE STRENGTH
    NDC 10019-075-87, 2000 MG – 100 Ml IntraVia Bags

13. The description of the BREVIBLOC INJECTION in the **HOW SUPPLIED** section has been changed from:

    NDC 10019-015-01, 100 mg – 10 mL Ready-to-use Vials, Box of 20

    To:

    NDC 10019-115-01, 100 mg – 10 mL Ready-to-use Vials, Package of 25

This supplement proposes the following changes to the container labeling:

<u>10 mL Ready-to-use Vial Label</u>

1. Changed the NDC number from:

   10019-015-71

To:

10019-115-39.

2. Changed the strength description from:

   100 mg/10 mL (10mg/mL)

   To:

   100 mg/10 mL
   (10mg/mL)

3. Moved the "Rx only" from the third line of text below the lavender band with the drug name to immediately below the lavender band with the drug name.

4. Inserted "Iso-Osmotic" on the line below "FOR INTRAVENOUS USE"

5. Deleted the following:

   "Each mL contains 10 mg Esmolol Hydrochloride and Water for Injection, USP. Buffered with Sodium Acetate Trihydrate, USP and Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added to adjust pH to 5.0 (range 4.5-5.5).

6. Moved and changed component code from:

   "400-409-04" above the bar code

   To:

   "460-325-00" below the bar code

7. Changed the bar code and corresponding numbers below the bar code.

<u>25 X 10 mL Vials Tray Label</u>

1. Changed the NDC number from:

   10019-015-71

   To:

   10019-115-01

2. Changed the quantity and description from:

   20 X 10 mL Ready-to-use Vials

   To:

   25 X 10 mL Ready-to-use Vials

3. Changed product description from:

Each mL contains 10 mg Esmolol Hydrochloride and Water for Injection, USP. Buffered with Sodium Acetate Trihydrate, USP and Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added to adjust pH.

To:

Each mL contains 10 mg Esmolol Hydrochloride and 5.9 mg Sodium Chloride, USP in Water for Injection, USP. Buffered with Sodium Acetate Trihydrate, USP and Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added to adjust pH to 5.0 (range 4.5-5.5).

4. The storage guidelines have been changed from:

   Store at controlled room temperature 15°-30°C (59°-86°F).

   To:

   Store at 25°C (77°F). Excursions permitted to 15°-30°C (59°-86°F).

5. Inserted "Iso-Osmotic" on the line below "Single dose Vials"

6. Moved manufacturing information from below the line that states "discard unused portion" to below the line that states "FOR INTRAVENOUS USE ONLY".

7. Added the phrase, "registered in the United States Patent and Trademark Office." following the phrase, "Baxter and Brevibloc are trademarks of Baxter International Inc."

8. Moved and changed the component code from:

   400-281-04

   To:

   460-326-00

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the proposed draft labeling included in your October 24, 2002 submission. Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert and immediate container and carton labels submitted October 24, 2002) with the following change to the immediate container label:

1. The immediate container label should contain the composition statement as it is in the current container label:

   Each mL contains 10 mg Esmolol Hydrochloride and 5.9 mg Sodium Chloride, USP in Water for Injection, USP. Buffered with Sodium Acetate Trihydrate, USP and Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added to adjust pH to 5.0 (range 4.5-5.5).

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-021". 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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