CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-386/S-021

Administrative Documents

RHPM Review of Draft Labeling
NDA19-386/S-021

Date of Submissions:	October 24, 2002
Date of Review:	December 3, 2002
Applicant Name:	Baxter Healthcare Corporation, Anesthesia & Critical Care
Product Names:	Brevibloc Injection 10 mg/mL in 10 mL ready-to-use vials (19-386/S-021)

Evaluation:
This submission 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. This commitment is 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 the at the supplement(s) will be submitted.

Baxter Healthcare Corporation, Anesthesia & Critical Care proposes the following labeling 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 312mOsmol/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** section, **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. In 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. In the **DOSAGE AND ADMINISTRATION** section, **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. In the **DOSAGE AND ADMINISTRATION** section, **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** section, **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** section, **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 in the **DOSAGE AND ADMINISTRATION** section, **Directions for Use of the 10 mL Ready-to-use Vial (10 milligrams/mL)** 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

Baxter Healthcare Corporation, Anesthesia & Critical Care proposes the following labeling 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.

Per the chemistry review, the following change is to be made 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).

Recommendation:

An approval letter should issue be issued for supplement 021 as set forth under 21 CFR 314.70 (b) (3) [Any change in labeling].

Melissa Robb, RHPM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Melissa Robb
2/26/03 09:47:35 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Microbiology (HFD-805) for **Micro. Consult.**
Attn: Dr. Peter Cooney

FROM: JV Advani (HFD-110)

DATE: **12/18 /02**	IND NO:	NDA NO. 19-386	TYPE OF DOCUMENT: Supplements SCF-021 Prior Approval Supplement	DATE OF DOCUMENT: 10/24/02

NAME OF DRUGS: Brevibloc Premixed Injection, 10 mg/mL in 10 mL in ready to use vials	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: January 31,03

NAME OF FIRM: **Baxter Healthcare Corporation**

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This supplement is filed for a new formulation with reduced overage of active ingredient. The vials are ——— in place of the currently used ——— vials. Micro review for this ——— change is required.

Thanks.

SIGNATURE OF REQUESTER: JV Advani	METHOD OF DELIVERY (Check one): i E- MAIL X☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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
Director, Regulatory Affairs
95 Spring Street
New Providence, NJ 07974

Dear Ms. Jambhekar:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Brevibloc (esmolol HCl in sodium chloride) Injection 10 mg/mL in 10 mL ready-to-use vials

NDA Number: 19-386

Supplement number: 021

Date of supplement: October 24, 2002

Date of receipt: October 25, 2002

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 24, 2002 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products,
HFD-110
Attention: Document Room 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
HFD-110
Attention: Document Room 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any question, please contact:

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

Sincerely,

/S/

Zelda McDonald
Chief, Project Management Staff
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/

Zelda McDonald
12/13/02 03:24:47 PM