CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 19-386/S-022

Trade Name: Brevibloc

Generic Name(s): (Esmolol hydrochloride in sodium chloride)

Sponsor: Baxter Healthcare Corporation

Agent:

Approval Date: May 28, 2003

Indication: Short-Term control of heart rate in patients with abnormally fast heart rhythms such as artrial fibrillation, atrial flutter or sinus tachycardia.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386 / S-022

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-386/S-022

Approval Letter(s)

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** CONCENTRATE:

   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
5/28/03 04:23:46 PM

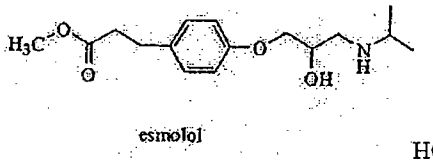
CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-386/S-022

Chemistry Review(s)

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19–386
3. Name and Address of Applicant (City & State) Baxter Pharmaceutical Products Inc. 95 Spring Street New Providence, NJ 07974		4. Supplement(s) Number(s) Date(s) SCM/022 01/28/03
5. Drug Name Brevibloc	6. Nonproprietary Name Esmolol HCl	7. Amendments & Other (reports, etc) Dates
8. Supplement Provides For: New product formulation double strength (20 mg/mL) Premixed Injection (esmolol HCl in sodium chloride) in a ready-to-use 5 mL glass vials.		
9. Pharmacological Category Anti–adrenergic (β receptor)	10. How Dispensed ☒Rx ☐OTC	11. Related IND(s)/ NDA(s)/DMF(s) DMFs [redacted]
12. Dosage Form(s) Intravenous injection	13. Potency(ies) 20 mg/mL in 5 mL vial total amount 100 mg	
14. Chemical Name and Structure (±) methyl p–[2–hydroxy–(isopropylamino)propoxy] hydrocinnamate hydrochloride Molecular weight: 331.8 Empirical formula: $C_{16}H_{25}NO_4$ .HCl  esmolol HCl		15. Records/Reports Current ☒Yes ☐No Reviewed ☒Yes ☐No

16. **Comments:**
This double strength (DS) 20 mg/mL qualitative formulation is same as the approved (single strength [SS]) 10 mg/mL Brevibloc Premixed injection in 5 mL vial, including the proposed reduction in the overage of esmolol to 4% (refer S-019 dated 9/30/02). Firm has provided 3 months stability data in the ready to use formulation in the 5 mL containers. Firm has also provided the manufacturing formula and executed batch records for double strength 20 mg/mL, in 5 mL vial. Firm has provided the revised labeling with relevant changes. Firm has provided the Environment Assessment Categorical Exclusion Certification.

Cont'd

17. **Conclusions and Recommendations**
This P.A. supplement may be approved from the standpoint of chemistry, microbiology, and draft labeling. Refer microbiology and draft labeling reviews filed with this supplement. There are no new establishments sites used for manufacturing this new Brevibloc double strength premixed injection.
The need for this double strength 20 mg/mL, in addition to the sponsor's existing single strength (SS) 10 mg/mL formulation was also recommended by the Agency on Jan.05, 2001.

18. **REVIEWER**

Name	Signature	Date Completed
JV Advani		May 05, 2003

4 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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/s/

J. V. Advani
5/22/03 08:25:25 AM
CHEMIST

Kasturi Srinivasachar
5/22/03 05:29:24 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-386/S-022

Microbiology Review(s)

Product Quality Microbiology Review

Review for HFD-110

May 22, 2003

NDA: 19-386/SCM-022

Drug Product Name
Proprietary: Brevibloc Double Strength Injection
Non-proprietary: esmolol HCl in sodium chloride
Drug Product Classification: for treatment of tachycardia

Review Number: 1

Subject of this Review
Submission Date: January 28, 2003
Receipt Date:
Consult Date: January 31, 2003
Date Assigned for Review: March 24, 2003

Submission History (for amendments only):

Applicant/Sponsor
Name: Baxter Healthcare Corporation
Address: 95 Spring Street
New Providence, NJ 07974
Representative: Priya Jambhekar, Dir. Reg. Affairs
Telephone: (908) 286-7215

Name of Reviewer: James L. McVey

Conclusion: This supplemental application to add ——————— 5 mL vials of 20 mg/mL Brevibloc to the current production done at ——————— is recommended for approval from a product quality microbiology perspective.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** Prior Approval

2. **SUPPLEMENT PROVIDES FOR:** A new double strength formulation (20 mg/mL). The double strength formulation in 5 mL vials is identical to the formulation approved on January 27, 2003 for Brevibloc double strength in 100 mL bags.

3. **MANUFACTURING SITE:** [redacted]

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 20 mg/mL in a 5 mL ready–to–use vial for IV administration.

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** beta blocker

B. **SUPPORTING/RELATED DOCUMENTS:**

C. **REMARKS:** [redacted]

filename: 19386s22r1

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended for approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – None. The applicant has committed to establishing holding times during initial production.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – [redacted]

B. Brief Description of Microbiology Deficiencies – None.

C. Assessment of Risk Due to Microbiology Deficiencies - Minimal risk to patient health is perceived from implementation of this supplement.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Review Microbiologist. J.L. McVey
Microbiology Supervisor. P.H. Cooney

C. CC Block

cc:
DFS
HFD- 805/McVey/19386s22r1

4 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Acceptable

F.3. Microbial Limits Testing – N.A.

G. LABELING .

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: None.

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

/s/

James McVey
5/22/03 10:52:23 AM
MICROBIOLOGIST

Peter Cooney
5/23/03 01:00:31 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-386/S-022

Administrative/Correspondence

RHPM Review of Draft Labeling
NDA 19-386/S-022

Date of Submissions:	January 30, 2003
Date of Review:	February 7, 2003
Applicant Name:	Baxter Healthcare Corporation, Anesthesia & Critical Care
Product Names:	Brevibloc Double Strength Injection, 20 mg/mL, in 5mL ready-to-use vials

Evaluation:
This submission is to market a Double Strength formulation in 5 mL vials, identical to the formulation that was approved on January 27, 2003 for Brevibloc Double Strength bags, packaged in 100mL bags.

Baxter Healthcare Corporation, Anesthesia & Critical Care proposes the following labeling 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** CONCENTRATE:

   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.

According to a review by Dr. Advani on May 22, 2003, this supplement can be approved from the standpoint of chemistry, microbiology, and draft labeling.

Dr. Advani noted that the following changes would have to be made for approval of the supplement:

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".

Recommendation:

An approval letter should issue for these supplements 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
5/28/03 04:28:45 PM
CSO

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. 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 hydrochloride in sodium chloride) Double Strength Injection, 20 mg/mL, in 5 mL ready to use glass vials

NDA Number: 19-386

Supplement number: 022

Date of supplement: January 28, 2003

Date of receipt: January 30, 2003

This supplemental application propose vial and carton labeling for the new DS product formulation, and also proposes revised package insert to reflect the new, approved, isotonic formulation (addition of sodium chloride), as well as addition of the DS 5 mL vials.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 31, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 30, 2003.

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,

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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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
2/13/03 11:30:28 AM