CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-386/S018

Trade Name: Brevibloc Injection

Generic Name: Esmolol Hydrochloride

Sponsor: Baxter Pharmaceutical Products Inc.

Approval Date: February 16, 2001

Indications: 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/S018

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
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Labeling	
Medical Review(s)	
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Microbiology Review(s)	X
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S018

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-386/S-018

Baxter Pharmaceutical Products, Inc.
Attention: Ms. Priya Jambhekar
95 Spring Street
New Providence, NJ 07974

Dear Ms. Jambhekar:

Please refer to your supplemental new drug application dated August 30, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brevibloc Premixed Injection (esmolol HCl in sodium chloride) in 2500 mg/250mL IntraVia Containers.

We acknowledge receipt of your submissions dated January 12, and February 2 and 9, 2001. Your submission of January 12, 2001 constituted a complete response to our December 29, 2000 action letter.

This supplemental new drug application provides for a premixed injection packaged in 250 mL IntraVia containers (made of PL 2408 plastic bags with laminated foil over-pouch) containing two ports. In addition, the word, "Injection" has been replaced with, "Concentrate" on the Ampul Label with Flag and the Ampuls Tray Label and the phrase, "Ready-to-Use" has been added to the Vial Label and Vials Tray Carton.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling for the IntraVia Containers (package insert and immediate container labels) included in your January 12, 2001 submission and the vial and ampul immediate container labels included in your February 2, 2001 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

When you make your production quantities of the labels, please change, "sodium acetate" to "sodium acetate trihydrate" on the Ampuls Tray Label and, to be consistent, add the amounts of the inactive ingredients to the labels that do not have them already.

We remind you of your postmarketing study commitments in your submissions dated January 12 and February 9, 2001. These commitments are listed below.

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

2. Baxter will tentatively reduce the specifications of ——— in the drug product specifications from ———— Baxter PPI will finalize these specifications after reviewing the 24 month stability data that will be available by August 2002.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, 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 the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333.

Sincerely,

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Raymond Lipicky
2/16/01 08:35:08 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/018

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-386/S-018

Baxter Pharmaceutical Products, Inc.
Attention: Ms. Priya Jambhekar
95 Spring Street
New Providence, NJ 07974

Dear Ms. Jambhekar:

Please refer to your supplemental new drug application dated August 30, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brevibloc (esmolol HCl in sodium chloride) Premixed Injection in 2500 mg/ 250 mL IntraVia Containers.

We acknowledge receipt of your submissions dated November 20 and 28, and December 5, 2000.

This supplement provides for a premixed injection packaged in 250 mL IntraVia containers (made of PL 2408 plastic bags with laminated foil over-pouch) containing two ports. Included with the submission is revised draft labeling describing this change as well as recommendations by the Institute for Safe Medication Practices.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up labeling (text for the package insert) and immediate container labeling included in your November 28, 2000 submission. We also have the following additional requests:

1. Please re-evaluate the necessity for the high overage (10%) of the active ingredient in the drug product and provide a commitment either to eliminate or significantly reduce it in a timely manner. We currently do not allow overages unless justified by unavoidable manufacturing losses.
2. [redacted]
3. [redacted]

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

We believe that the ——————— Brevibloc, Please note that the attached draft labeling for the ——————— We have made many changes to the enclosed marked-up draft that we think will avoid medication errors, while allowing the 10 mL Ampul (250 mg/ml) to remain on the market. We invite you, at your earliest convenience, ———————

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call:

Ms.Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333.

Sincerely,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

/s/

Norman Stockbridge
12/29/00 02:24:50 PM
For RJ Lipicky

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	908-286-7269
Attention:	**Ms. Priya Jambhekar**
Company Name:	**Baxter**
Phone:	908-286-7215
Subject:	**Approvable Letter**
Date:	12/29/00
Pages including this sheet:	25

From: **Zelda McDonald**
Phone: **301-594-5333**
Fax: **301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

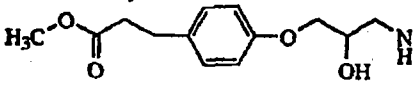
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S018

CHEMISTRY REVIEW(S)

NDA 19–386/018 amendments

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) SCP/018 08/30/00
5. Drug Name Brevibloc	6. Nonproprietary Name Esmolol HCl	7. Amendments & Other (reports, etc) Dates Amendments - Dated 01/12/01 02/02/01 02/09/01
8. Supplement Provides For: Packaging of the currently approved 10 mg/mL Brevibloc premixed Injection (Esmolol hydrochloride in sodium chloride) in an additional configuration, 250 mL in IntraVia Containers (made of PL 2408 plastics bags with laminated foil overpouch) containing two ports.		
9. Pharmacological Category Anti–adrenergic (β receptor)	10. How Dispensed ☒Rx ☐OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Intravenous injection	13. Potency(ies) 250mg/mL 10mL amp 10 mg/mL 10mL vial	
14. Chemical Name and Structure methyl p–[2–hydroxy–(isopropylamino)propoxy] hydrocinnamate hydrochloride  HCl		15. Records/Reports Current ☒Yes ☐No Reviewed ☒Yes ☐No

16. **Comments:**

This review is of a prior approval supplement for a premixed injection packaged in 250 mL IntraVia containers. These amendments are in response to our approvable letter of December 29, 2000.

Firm is committing that they will evaluate the overage issue and also will evaluate tentatively proposed specifications of —— for the degradation product ————

On our request, firm has further clarified the phase 4 commitments and has included a specific time lines to completion as under:

Commitment 1: Firm will provide detailed plan of action within 6 months by 08/2001 for re-evaluation of the formulations for Brevibloc Premixed in 250 mL bags and Injection in 10 mL vials. And plan of action for the concentrate in ampuls will follow within six months by 02/2002.

Commitment 2: Firm will review the 24-month stability data on the ——of Brevibloc Bag by August 2002 to confirm the proposed specification of ——for the degradation product, ————

Labeling: Firm states that the previous package insert has listed one of the in actives sodium acetate trihydrate as sodium acetate by mistake. The proposed revised package insert now has this ingredient correctly mentioned as sodium acetate trihydrate. There is no change in formulation but correct representation of the inactive ingredient.

Cartons labeling: It's noticed that In one of the cartons labeling submitted in amendment of 1/12/01, has inactive ingredient sodium acetate mentioned instead of corrected representation as sodium acetate trihydrate. Also in some cartons labels there is mention of the amounts of inactive ingredients and some carton labels no amounts of in active ingredients are described. Firm must correct these discrepancies in package/cartons labels in FPL.

17. Conclusions and Recommendations

Approval letter may be issued.

18. REVIEWER

Name	Signature	Date Completed
JV Advani		February 13, 2001

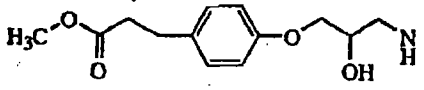
NDA 19–386/018 amendments

Distribution:	Original Jacket	Reviewer	Division File	CSO

/s/

J. V. Advani
2/13/01 02:32:38 PM
CHEMIST

Kasturi Srinivasachar
2/13/01 03:15:52 PM
CHEMIST

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) SCP/018 08/30/00
5. Drug Name Brevibloc	6. Nonproprietary Name Esmolol HCl	7. Amendments & Other (reports, etc) Dates Amendment of 11/20/00 Amendment of 11/28/00 Amendment of 12/05/00* (*withdrawal of Aibonito PR site)
8. Supplement Provides For: Packaging of the currently approved 10 mg/mL Brevibloc premixed Injection (Esmolol hydrochloride in sodium chloride) in an additional configuration, 250 mL in IntraVia Containers (made of PL 2408 plastics bags with laminated foil overpouch) containing two ports.		
9. Pharmacological Category Anti–adrenergic (β receptor)	10. How Dispensed ☒Rx ☐OTC	11. Related IND(s)/ NDA(s)/DMF(s) DMF 11691
12. Dosage Form(s) Intravenous injection	13. Potency(ies) 250mg/mL 10mL amp 10 mg/mL 10mL vial	
14. Chemical Name and Structure methyl p–[2–hydroxy–(isopropylamino)propoxy] hydrocinnamate hydrochloride  HCl		15. Records/Reports Current ☒Yes ☐No Reviewed ☒Yes ☐No

16. **Comments:**
Firm has provided the 6 months stability data in the ready to use formulation in the 250 mL IntraVia containers. Firm has also provided the manufacturing formula and executed batch records for new configuration, 10 mg/mL, 250 mL non-PVC bag. Firm has provided the revised labeling with relevant changes

Cont'd

17. **Conclusions and Recommendations**
This P.A. supplement may be approved from the stand point of chemistry and draft labeling. Refer microbiology and draft labeling reviews filed with this supplement.. All establishments sites are acceptable. (Firm has withdrawn plastic container assembly site in Aibonito, PR, amendment of 12/05/00)
Copy of acceptable EER is attached. Following recommendation were made in teleconference with the firm on 11/27/00.
1) Storage statement of the inner plastic bag and outer foil pouch should be changed to read "Store at 25°C (77°F);excursion permitted to 15-30°C (59°-86°F). See USP Controlled Room Temperature .
2) The high overage ——— and acceptance criteria ——— for ——— are not justified based on the stability data presented.
Firm has now revised the bag labels and included the storage statement as requested (amendment 11/28/00).

However the firm has to revise also the storage statement in the package insert.
Firm is committing that they will evaluate the overage issue and specifications.

18. **REVIEWER**

Name	Signature	Date Completed
JV Advani		Nov. 28, 2000

Distribution: ☒ Original Jacket ☒ Reviewer ☒ Division File ☒ CSO

4 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

/s/

J. V. Advani
12/20/00 04:24:25 PM
CHEMIST

Kasturi Srinivasachar
12/20/00 05:22:07 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S018

MICROBIOLOGY REVIEW

REVIEW TO HFD-110
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF/HFD-805
MICROBIOLOGY REVIEW #1 OF NDA

15 December 2000

A. 1. NDA: 19-386/SCP-018

2. TYPE OF SUPPLEMENT: Prior Approval

3. SUPPLEMENT PROVIDES FOR: A ready to use concentration of the drug product in a new container (LVP).

4. APPLICANT/SPONSOR: Baxter Pharmaceutical Products, Inc.
95 Spring Street
New Providence, New Jersey 07974

5. MANUFACTURING SITE: Baxter Healthcare Corporation
Highway 221 North
Marion, North Carolina 28752

6. DRUG PRODUCT NAME:
Proprietary: Brevibloc®
Nonproprietary: Esmolol hydrochloride
Drug Priority Classification:

7. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 250mL plastic bag for IV, 10 mg.mL

8. METHOD(S) OF STERILIZATION: ————————

9. PHARMACOLOGICAL CATEGORY:

B. 1. DOCUMENT/LETTER DATE: August 30, 2000
2. RECEIPT DATE: August 31, 2000
3. CONSULT DATE: September 5, 2000
4. DATE OF AMENDMENT: na
5. ASSIGNED FOR REVIEW: October 23, 2000
6. SUPPORTING/RELATED DOCUMENTS: DMF 11,691

C. REMARKS: The validation information for the ———————— is located in Baxter DMF 11,691.

D. CONCLUSIONS: This submission is recommended for approval on the basis of product quality microbiology.

Bryan S. Riley, Ph.D.
Microbiology Reviewer

cc.: Original NDA 19-386
HFD 110/Division File
HFD 110/Z. McDonald
HFD 110/J. Advani
HFD 805/Consult File
HFD 805/B. Riley

Drafted by: Bryan Riley, Ph.D.
R/D initialed by: Peter Cooney, Ph.D.

filename: C:\data\data\word\nda\s\19386s18

2 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

/s/

Bryan Riley
12/22/00 12:25:36 PM
MICROBIOLOGIST

Peter Cooney
12/22/00 01:41:59 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S018

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

RHPM Review of Final Printed Labeling
NDA 19-386/S-018

Date of Submission:	January 12, 2001
Date Received:	January 26, 2001
Date of Review:	January 26, 2001
Applicant Name:	Baxter Pharmaceutical Products Inc.
Product Name:	Brevibloc Premixed Injection (esmolol HCl in sodium chloride), in 2500 mg/250 mL IntraVia Containers

Evaluation:
This submission provides for final printed labeling revised to include a description of the new pre-mixed bag, Dosing and Administration instructions and How Supplied information for the pre-mixed bag. The changes are too extensive to list here. Except for a few minor editorial changes, the labeling is identical to the marked-up draft labeling that accompanied the December 29, 2000 approvable letter and the agreements made in the January 5, 2001 teleconference. The agreements per the teleconference are as follows:

It was agreed that the three dosage forms can be separated at the beginning of the labeling as Baxter had originally proposed, and the foot note regarding the tradenames can remain at the end of the labeling. Baxter will substitute "Concentrate" for "Injection" when describing the ampul, however, use of "Bolus" instead of "Injection" when describing the vial will be addressed in a future submission. The word "container" will be replaced by "bag" throughout the labeling. Although not mentioned in the minutes, we agreed with Baxter's proposal to include a patient information label that can be applied to the inner bag. Therefore, the sentence, "Fill out the patient information label supplied and apply to the inner bag" has been added to the DOSAGE AND ADMINISTRATION section.

There are no other changes from the last approved package insert.

The word, "Injection" has been replaced with, "Concentrate" on the Ampul Label with Flag and the Ampuls Tray Label.

The phrase, "Ready-to-Use" has been added to the Vial Label and Vials Tray Carton.

When Baxter makes the production quantities of the labels, they should change, "sodium acetate" to "sodium acetate trihydrate" on the Ampuls Tray Label and, to be consistent, add the amounts of the inactive ingredients to the labels that do not already have them. This will be requested in the approval letter.

Recommendation:
An approval letter should issue for this supplement as set forth under 21 CFR 314.70 (b) (3)(I) [Any change in labeling].

Zelda McDonald, RHPM

cc: orig. NDA
HFD-110
HFD-110/McDonald
HFD-110/Blount
HF-2

/s/

Zelda McDonald
2/20/01 03:46:20 PM
CSO

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	908-286-7269
Attention:	**Ms. Priya Jambhekar**
Company Name:	Baxter
Phone:	908-286-7215
Subject:	Minutes of 1/5/01 Telecon
Date:	1/23/01
Pages including this sheet:	4

From:	**Zelda McDonald**
Phone:	**301-594-5333**
Fax:	**301-594-5494**

YOU ARE RESPONSIBLE FOR NOTIFYING US OF ANY SIGNIFICANT DIFFERENCES IN UNDERSTANDING YOU MAY HAVE REGARDING THE MEETING OUTCOMES (AS REFLECTED IN THE MINUTES).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

cc:
Orig.
HFD-110
HFD-110/McDonald/Matthews

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — Public Health Service
Division or Cardio-Renal Drug Products — Memorandum

Date : December 27, 2000
From : Director, Division of Cardio-Renal Drug Products, HFD-110
Subject : Approvability of NDA 19-386, Esmolol Premix (250 ml/10mg per ml), Baxter Healthcare
To : NDA File

Baxter has formulated a **250 ml premix** of esmolol (10mg/ml) in a sterile, isotonic solution contained in a bag meant to be used for infusion of esmolol without the need for dilution. Previously, there was a **10 ml Ampul** (containing a total of 2,500 mg esmolol, 250 mg/ml) that required on-site dilution to prepare a similar solution for infusion, except that the on-site health care professionals might not have used an isotonic solution for dilution.

There is a **10 ml vial** (containing a total of 100 mg esmolol, 10 mg/ml) that was used for giving "loading doses", one minute infusions. The current premix container has a port that can be used for getting the "loading doses" directly from the same container that is being used for longer duration infusions.

From a manufacturing and controls vantage point, everything is in order (except as noted in the "approvable" letter. Everything is order except for labeling.

OPDRA has provided an insightful review and points out that the use of esmolol has been associated with an incidence of medication errors that were associated with the use of the concentrated solution (250 mg/ml) solution for infusion without appropriate dilution. Indeed, these errors did occur but with apparently decreasing frequency. The premix bag for infusion eliminates the need for on-site formulation of 10 mg/ml infusion formulation.

The need for an available formulation of esmolol that contains greater than a 10 mg/ml concentration of esmolol.

There are certainly times in critical care medicine when the total volume of solution infused intravenously is critical. Although all loading and chronic infusion dosing is outlined in the form of using a 10/mg/ml concentration, dosing is specified in terms of micrograms or milligrams/kg/minute. For heavier patients, when dosing is specified in terms of ml/minute, this can amount to as much as 132 ml/hour. Guessing that in a patient with renal shutdown and recent onset atrial fibrillation that at least a 6 hour treatment with esmolol might be needed, the esmolol treatment alone (using 10 mg/ml concentrations) would exceed the fluid limits that are allowed over an entire 24 hour day.

So labeling is important here. Labeling is a guessing game. It is a guess as what language communicates what, and what language prevents errors. Over the years, I think the data indicate that the FDA's guesses (along with Baxter) have improved language and that errors have decreased (5 reports in interval 1997-1999, compared to 10 in the interval 1992- 1994). The premix formulation should make that even better.

Labeling Changes That Are Needed

Page 1 of draft package insert

The order (that is the appearance from the top of the page) of formulations should be:

3 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

/s/

Norman Stockbridge
12/29/00 02:13:07 PM
MEDICAL OFFICER
For RJ Lipicky

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — **Public Health Service**
Division or Cardio-Renal Drug Products — **Memorandum**

Date : December 28, 2000
From : Director, Division of Cardio-Renal Drug Products, HFD-110
Subject : Approvability of NDA 19-386, Esmolol Premix (250 ml/10mg per ml), Baxter Healthcare
Addendum to Approvability Memo of 12/27/00
To : NDA File

Upon looking at the revised draft labeling, based on my 12/27/00 memorandum, it appears to me that there is an even better way to avoid the problems of medication errors that occur simply because of similar names. Indeed there are only two formulations of esmolol:

10 mg/ml, which comes in total volumes of 10 ml or 250 ml

and

250 mg/ml, which comes in a total volume of 10 ml.

Part of the problem is that both 10 ml volumes are called Brevibloc ™.

Indeed if both the 10 and 250 ml volumes of 10 mg/ml were called Brevibloc ™ Premix (as they are now classified in the Division marked-up draft labeling) and the 250 mg/ml ampul was called Brevibloc ™ Concentrate, a semantic and confusing issue might be resolved. I think this should be suggested to Baxter in the approvable letter.

Baxter can, as they evaluate inventory and manufacturing schedules, submit another supplement that changes nothing other than container labeling and the name in the package insert.

For now, the current supplement is approvable according to the marked up version of the package insert.

The approvable letter should say:

_____ . We have made many changes to the enclosed marked-up draft that we think will avoid medication errors, while allowing the 10 mL Ampul (250 mg/ml) to remain on the market. _____

There are also a few corrections that need to be made to the 12/27/00 draft package insert.

Page 1 Brevibloc Injection, the last sentence under that heading should read;

SEE DOSAGE AND ADMINISTRATION: Directions for use of the 10 mL Ampul (250 mg/mL).

The directions for use of the 10 mL Ampul (250 mg/mL) is new, but is the appropriate reference for where to look.

Page 2 Bottom of the page, in the section for Brevibloc injection, after the 2500mg, 10 mL Ampul – where it describes the esmolol concentration should read:

Each mL 250 mg Esmolol Hydrochloride instead of esmolol HCL,

After the sentence that ends with "...hydrochloric acid added, as necessary, to adjust pH to 3.5-5.5.", there should be a repeat warning and instructions for where to look:

NOT FOR DIRECT INTRAVENOUS USE. AMPUL MUST BE DILUTED PRIOR TO ITS INFUSION. SEE DOSAGE AND ADMINISTRATION: Directions for use of the 10 mL Ampul (250 mg/mL).

Page 10 Last paragraph, 1st sentence that reads Maintenance infusion may be continued for as long as — There should be a sentence before it and the existing sentence should be modified so the first two sentences of the paragraph would read:

In the absence of loading doses, constant infusion of a single concentration of esmolol reaches pharmacokinetic and pharmacodynamicsteady-state in about 30 minutes. Maintenance infusions (with or without loading doses) may be continued for as long as 24 hours.

Elapsed
Time
(Minutes)

Page 14 Directions for Use of the Premixed Bag. First paragraph, all of the BREVIBLOC PREMIXED ™ need to be changed to BREVIBLOC ™ PREMIXED.

Then it is ready to go. Dr. Stockbridge will sign this and the previous memorandum as well the approvable letter.

/s/

Norman Stockbridge
12/29/00 02:15:03 PM
MEDICAL OFFICER
For RJ Lipicky

Teleconference Minutes

Telecon Date:	January 5, 2001
Date Requested:	Our request: January 3, 2001
NDA:	19-386/S-018
IND:	20,015
Sponsor:	Baxter
Type:	Guidance
Classification:	C

Telecon Chair:	Raymond Lipicky, M.D.
Telecon Recorder:	Zelda McDonald
External Participant Lead:	Priya Jambhekar

FDA:

Raymond Lipicky, M.D.	Director, Div. of Cardio-Renal Drug Products, HFD-110
Zelda McDonald	RHPM, HFD-110

Baxter:

Priya Jambhekar	Director, Regulatory Affairs
Marc Hoffman, MD.	Director, Drug Safety and Clinical Research
Raul Trillo, M.D.	Senior Director, Marketing
Kent Allenby Sr., M.D.	Vice President, Clinical Research and Medical Affairs
Carl Strotz	Manager, Labeling

Background:
Baxter submitted a chemistry supplement with labeling on August 30, 2000 that provided for a pre-mixed injection packaged in 250 mL IntraVia Containers. Approvable letter with marked-up labeling for this supplement issued on December 29, 2000. The main thrust of this supplement was to avoid medication errors that can/have occur(red) with the ampul that requires dilution before use.

In addition, Baxter submitted proposals for a ———————————————— revised statistical plan for their proposed Brevibloc pediatric study (20,015-004) on December 22 and 27, 2000 respectively. The Division requested this telecon to discuss the supplement and Baxter's two proposals.

Telecon:

1. The Agency grouped the 10 mL vials and 250 mL IntraVia containers as a pre-mixed dosage form and separated that ampuls form this presentation in the mark-up labeling that accompanied the approvable letter. Baxter believes that the grouping of the vials and containers under the one premixed group could lead to some confusion. Baxter believes that each Brevibloc presentation is unique, and asked if they could be represented separately.

    - Dr. Lipicky agreed.

    - Baxter stated that they liked the idea of changing "Brevibloc Injection" to "Brevibloc Concentrate for the ampul and asked if Dr. Lipicky had any further suggestions to prevent medication errors.

- Dr. Lipicky suggested that the vial should be designated ———— but that should not be done as part of supplement 18.

2. Baxter pointed out that the terms, "bags" and "containers" are both used to describe the Intravia formulation and asked if one should be used consistently and, if so, which one.

   - Dr. Lipicky said, —— should replace ————

3. Dr. Lipicky stated that use of the Trademark symbol after the word ———— in Brevibloc ———— is not acceptable because ————is a generally accepted and commonly used term that is used by various sponsors and reference texts to describe this type of ————

   - Baxter stated that they were not trademarking ———— but the two words "Brevibloc ———— They agreed to remove the symbol but asked if they could retain the footnote in the labeling that states———— is a trademark of Baxter. Dr. Lipicky agreed.

4. ————

5. In their Proposal for modification of the pediatric protocol submitted for pediatric exclusivity submmitted on December 27, 2000, [redacted]

Dr. Lipicky asked if the PK studies would be done in another age group (other than 6 to 16 year olds). Baxter said they planned to.

Action Items:

1. Baxter will submit final printed labeling for Supplement 18. It was agreed that the three dosage forms can be separated at the beginning of the labeling and that the foot note regarding the tradenames can remain at the end of the labeling. Baxter will substitute "Concentrate" for "Injection" when describing the ampul, however, use of "Bolus" instead of "Injection" when describing the vial will be address in a future submission. Likewise the proposal for use of the [redacted] will be a separate submission.

2. Baxter will rethink the pediatric proposal and discuss any revised proposal in a future telecon.

Signature minutes preparer: _____

Concurrence, Chair: _____

orig. NDA
HFD-110
HFD-110/McDonald
HFD-110/Matthews

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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
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CSO