CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-461/S-050

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-461/S-050

Baxter Healthcare Corporation
Attention: Ms. Marcia Marconi
Route 120 and Wilson Road
Round Lake, IL 60073

Dear Ms. Marconi:

Please refer to your December 10, 1999 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Hydrochloride in 5% Dextrose Injection in Viaflex® Plastic Container.

We acknowledge receipt of your submission dated April 25, 2001 that constitutes a complete response to our May 30, 2000 approvable letter.

This supplemental new drug application provides for final printed labeling revised as follows:

1. Under the **Description** section, the last two sentences have been changed from:

   > Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological standards for plastic containers as well as by tissue culture toxicity studies.
   >
   > to:
   >
   > Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials.

2. Under the **Precautions/Drug Interactions** subsection, "Amiodarone" has been added to the first sentence of the third paragraph.

3. After the **Pediatric Use** section, the following section has been added:

   > **Geriatric Use**
   > Clinical studies of Lidocaine Hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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 submitted final printed labeling (package insert included in your April 25, 2001 submission). Accordingly, the supplemental application is approved effective on the date of this letter.

At the time of your next printing, please make the following minor editorial corrections and include them in your annual report:

1) Under the **Precautions/Drug Interactions** subsection, in the first sentence of the third paragraph, the capital letter "A" in "Amiodarone" should be changed to lowercase letter "a."

2) Under 21 CFR 201.57(f), the information on pediatric and geriatric use should be provided in subsections under the **Precautions** section, rather than in sections. Therefore, the font size of the **Pediatric Use and Geriatric Use** section headers should be changed to that of the subsection headers.

3) Under **Geriatric Use**, there should be a comma after the word "range" in the last sentence.

4) The statement "Do not administer unless solution is clear and seal is intact" should be moved from the end of the **Geriatric Use** section to the end of the **Precautions/General** subsection.

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 contact:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 594-5311

Sincerely, /S/

{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

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

/s/

Raymond Lipicky
1/23/02 11:56:19 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
18-461/S-050

Approvable Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 30 2000

NDA 18-461/S-050

Baxter Healthcare Corporation
Attention: Ms. Marcia Marconi
Route 120 and Wilson Road
Round Lake, IL 60073-0490

Dear Ms. Marconi:

Please refer to your supplemental new drug application dated December 10, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Hydrochloride in 5% Dextrose Injection in Viaflex Plastic Container.

This supplement proposes the following change(s):

1. The last two sentences of the Description section have been changed from:

   Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di 2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological standards for plastic containers as well as by tissue culture toxicity studies.

   to:

   Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials.

2. Under Drug Interactions, "amiodarone" has been added to the first sentence of the third paragraph.

3. The following subsection has been added after the Pediatric Use subsection:

   Geriatric Use
   Clinical studies of Lidocaine Hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

We have completed the review of this application, 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 submitted draft labeling (package insert included in your December 10, 1999 submission).

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 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

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

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, please call:

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

Sincerely,

5/30/00

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

cc:
Archival NDA 18-461S-050
HFD-110/Div. Files
HFD-110/Z.McDonald
DISTRICT OFFICE

Drafted by: ZM/May 8, 2000
Initialed by: J Advani/5/11/00
K Srinivasachar/5/8/00
A Proakis/5/8/00
C Resnick/5/8/00
S Rodin/5/15/00
A Karkowsky/5/15/00
N Morgenstern/5/24/00
Final: asb/5/25/00
Filename: 18-461s050(ae).doc

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
18-461/S-050

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology/Biopharmaceutics Review

APR 21 2000

NDA: 18461 Submission Dates: December 10, 1999
Lidocaine hydrochloride, SLR-050, SLR-049 October 21, 1999
Baxter Healthcare Corp.

Reviewer: Gabriel J. Robbie

Type of Submission: This is a geriatric labeling supplement for lidocaine hydrochloride in 5% dextrose injection in Viaflex plastic container

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BACKGROUND:

Lidocaine hydrochloride and 5% dextrose injection is intended for use in the management of ventricular arrhythmias. The sponsor intends to incorporate information pertaining to lidocaine and 5% dextrose injection use in geriatric population in compliance with the Final Rule published in the Federal Register (August 27, 1998) requiring geriatric labeling information.

AMENDMENT:

1. The sponsor intends to add "Amiodarone" to the list of drugs in the PRECAUTIONS/Drug Interactions. This is because serum lidocaine concentration increased from 5.4 mg/L to 12.6 mg/L when amiodarone therapy was initiated concomitantly with lidocaine.

2. The following information is intended to be incorporated under Precautions/Geriatric Use subsection of the label.

Geriatric Use: Clinical studies of Lidocaine Hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

COMMENTS:

The Office of Clinical Pharmacology has reviewed the two amendments listed above. There is a trend toward decreased clearance of lidocaine in the elderly, however, the data from one study suggests that the decrease (≈35%) in clearance is only in heart failure patients (Clin Pharm Ther 37(4):381-386, 1985). In another study, decreased clearance was observed in elderly males (≈35% lower) and not in elderly females (J Cardiovas

Pharm 5(6):1093-1096, 1983). In view of such differences and the insufficient number of elderly subjects studied, the proposed geriatric amendment to the label is acceptable.

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics finds the proposed geriatric labeling supplement acceptable. No action is necessary at this time.

/S/ 4/21/00

Gabriel J. Robbie, Ph. D.

RD/FT by Emmanuel O. Fadiran, Ph. D., /S/ 4/21/2000

Cc: NDA 18461, HFD 110, HFD 860 (Mehta, Robbie), CDER document room: Attn: Biopharm(CDER)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-461/S-050

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-461/S-050

DEC 16 1999

Baxter Healthcare Corporation
Route 120 and Wilson Road; RLT-10
Round Lake, IL 60073

Attention: Marcia Marconi
Vice President, Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Lidocaine Hydrochloride in 5% Dextrose Injection in Viaflex Plastic Container

NDA Number: 18-461

Supplement Number: S-050

Date of Supplement: December 10, 1999

Date of Receipt: December 13, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 11, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Office of Drug Evaluation I
Attention: Document Control Room 5005
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products, HFD-110
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 18461/050
HFD-110/Div. Files
HFD-110/CSO/Diana Willard

S
12/15/99

filename: C:\WPWIN61\TEMPLATE\FDA\18461S50.WPD

SUPPLEMENT ACKNOWLEDGEMENT

B.P.C.
12-14-99

S
12/16/99

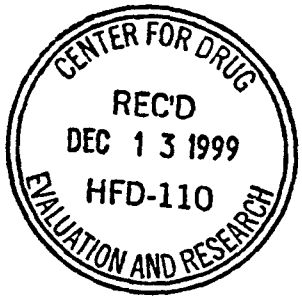
I.V. Systems Division
Regulatory Affairs

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

847.270.4637
Fax: 847.270.4668

ORIGINAL

Baxter



December 10, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
Attention: Document Control Room, HFD-110
1451 Rockville Pike
Rockville, MD 20852

NDA NO. 18461 REF. NO. 050
NDA SUPPL FOR SLR

RE: NDA 18-461 Lidocaine HCl in 5% Dextrose Injection in Viaflex® Plastic Container

-- Supplemental Application - Geriatric Labeling --

Ladies and Gentlemen:

Baxter Healthcare Corporation is submitting this supplemental application pursuant to the Final Rule published in the Code of the Federal Register on August 27, 1997, *Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in the Labeling*, vol. 62, No. 166, pages 45313 - 45326.

The content and format of this supplemental application is consistent with the draft Guidance for Industry, *The Content and Format for Geriatric Labeling*, dated December 1998.

We are adding the *Geriatric Use* subsection to the labeling in accordance with 21 CFR §201.57(f)(10)(ii)(A).

No user fees are included with this supplemental application because, at the present time, no fees are assessed for supplemental applications that do not contain clinical data.

DEC 10 199

ORIGINAL

4

Baxter

If you have any questions, please contact Beth Esche or myself at (847) 270-2577.

Sincerely,

Marcia Marconi (4.K-)

Marcia Marconi
Vice President, Regulatory Affairs
(847) 270-4637
(847) 270-4668 (FAX)

DEC 10 1999

5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-461/S-050

Administrative Documents

RHPM Review of Final Printed Labeling

Application:	NDA 18-461/S-050 Lidocaine Hydrochloride in 5% Dextrose Injection in Viaflex® Plastic Container
Applicant:	Baxter Healthcare Corporation
Document Date:	April 25, 2001
Receipt Date:	April 26, 2001

Background:

Baxter submitted this supplement (S-050) on December 10, 1999 to propose the establishment of a **Geriatric Use** section. This supplement was submitted in response to a Federal Register Notice of August 27, 1997 that amended the regulations governing the content and format of labeling for human prescription drug products to include information pertinent to the appropriate use of drugs in the elderly (persons aged 65 years and older) and to facilitate access to this information by establishing a "Geriatric Use" subsection in the labeling. Additionally, the **Description** section and **Precautions/Drug Interactions** subsection has been updated.

An approvable letter issued May 30, 2000 requesting final printed labeling that was identical to the draft labeling submitted on December 10, 1999.

Review:

This submission provides for final printed labeling, which is identical in content to the draft labeling submitted on December 10, 1999 per the May 20, 2000 approvable letter as follows:

1. Under the **Description** section, the last two sentences have been changed from:

   Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological standards for plastic containers as well as by tissue culture toxicity studies.

   to:

   Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials.

2. Under the **Precautions/Drug Interactions** subsection, "Amiodarone" has been added to the first sentence of the third paragraph.

3. After the **Pediatric Use** section, the following section has been added:

Geriatric Use
Clinical studies of Lidocaine Hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

On the IND/NDA Subsequent Submissions Review Transmittal sheet, Dr. Rodin NAI'ed this submission on January 10, 2000.

In his April 21, 2000 review, Dr. Robbie wrote: "The Office of Clinical Pharmacology and Biopharmaceutics finds the proposed geriatric labeling supplement acceptable. No action is necessary at this time."

Minor editorial errors were noted in this final printed labeling submission. Per a January 3, 2002 discussion with Dr. Stockbridge, he concurred that the following editorial corrections should be made:

1) Under the **Precautions/Drug Interactions** subsection, in the first sentence of the third paragraph, the capital letter "A" in "Amiodarone" should be changed to lowercase letter "a."

2) Under 21 CFR 201.57(f), the information on pediatric and geriatric use should be provided in subsections under the **Precautions** section, rather than in sections. Therefore, the font size of the **Pediatric Use** and **Geriatric Use** section headers should be changed to that of the subsection headers.

3) Under **Geriatric Use**, there should be a comma after the word "range" in the last sentence.

4) The statement "Do not administer unless solution is clear and seal is intact" should be moved from the end of the **Geriatric Use** section to the end of the **Precautions/General** subsection.

There are no other changes from the last approved package insert (approved September 18, 1998/ S-046).

Comments/Recommendations:

An approval letter should issue for this supplement as set forth under 21 CFR 201.57(f)(10)(ii)(A) [**Specific requirements on content and format of labeling for human prescription drugs/** *Geriatric Use*] and 314.70(b)(3)(i) [Any change in labeling]. The sponsor will be asked to make the above mentioned minor editorial corrections at the time of their next printing and to report these changes in their annual report.

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager

Cc: NDA 18-461
HFD-110
HFD-110/QNguyen

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

/s/

Quynh Nguyen
1/22/02 03:18:16 PM
CSO

RHPM Review of Draft Labeling
NDA 18-461/S-050

MAY 3 0 2000

Date of Submission: December 10, 1999
Date of Review: May 2, 2000
Applicant Name: Baxter Health Care Corporation
Product Name: 0.2, 0.4% and 0.8% Lidocaine and 5% Dextrose Injection
Evaluation:
This submission provides for draft labeling revised to provide for the addition of a Geriatric Use subsection, the addition of "amiodarone" to the drug interactions subsection and an update to the Description section as follows:

1. The last two sentences of the Description section have been changed from:

   Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di 2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological standards for plastic containers as well as by tissue culture toxicity studies.

   to:

   Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials.

2. Under Drug Interactions, "amiodarone" has been added to the first sentence of the third paragraph.

3. The following subsection has been added after the Pediatric Use subsection:

   Geriatric Use
   Clinical studies of Lidocaine Hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In his review dated April 21, 2000, Dr. Robbie concluded that the proposed geriatric changes are acceptable.

Recommendation:
An approvable letter should issue for this supplement as set forth under 21 CFR 314.70 (c) (i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction].

/S/
Zelda McDonald, RHPM

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