

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75852

CORRESPONDENCE

ANDA 75-852

AUG 2 2001

Baxter Pharmaceutical Products, Inc.
Attention: Priya Jambhekar
95 Spring Street
New Providence, NJ 07974-1143

Dear Madam:

This is in reference to your abbreviated new drug application dated April 28, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Milrinone Lactate Injection, 1 mg (base)/mL, packaged in 10 mL, 20 mL, and 50 mL single-dose vials.

Reference is also made to your amendments dated March 21, May 16, and June 20, 2001.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Primacor Injection of Sanofi Synthelabo, Inc., is currently subject to a period of patent protection which expires on November 26, 2001 (U.S. Patent No. 4,313,951, the "'951" patent). Your application contains a Paragraph III Certification to the '951 patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of the patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the '951 period has expired, i.e., currently November 26, 2001.

Because the Agency is granting a tentative approval for this application, please submit an amendment between 60 to 90 days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. An amendment should be submitted even if none of these changes were made. This submission should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

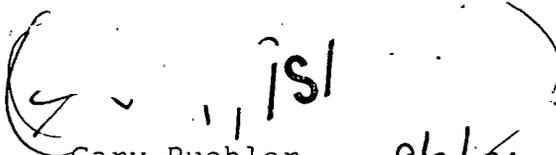
Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to November 26, 2001, you should amend your application accordingly.

Should you have any questions concerning the status of this application, please contact Bonnie McNeal, Project Manager, at 301-827-5849.

Sincerely yours,

A handwritten signature in black ink, appearing to read "G. Buehler", enclosed within a large, hand-drawn circular scribble.

Gary Buehler

8/2/01

Director

Office of Generic Drugs

Center for Drug Evaluation and Research

ANDA 75-852

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

JUN 2 2000]

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Milrinone Lactate Injection USP, 1 mg/mL in 10 mL, 20 mL and 30 mL Vials

DATE OF APPLICATION: April 28, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 1, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

[Handwritten signature]
[Handwritten initials]

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

*Labeling amendment
drafted 1/4/01
A. Bzyan*

Baxter

December 19, 2000

via Airborne overnight Express

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

ORIG AMENDMENT
N/A M



Attention: Mr. Gary Buehler
Acting Director, Office of Generic Drugs

re: **ANDA 75-852 Milrinone Lactate Injection, USP**
1 mg/mL in 10 mL, 20 mL, 50 mL Vials, in 5% Dextrose
Minor Amendment: Response to Deficiency Letter of 11/17/00

Dear Mr. Buehler:

Baxter Pharmaceutical Products Inc. [Baxter PPI] is submitting to the above ANDA, in duplicate, a response to a Deficiency Letter from the Agency dated November 17, 2000 (copy attached).

This submission is a complete response to the Agency's comments, which are addressed on an item-by-item basis. The Baxter PPI response is organized as follows:

The submission consists of 2 volumes; Volume 1 includes full responses to the Agency's Chemistry, Manufacturing, and Controls [CMC], and Labeling questions, and includes a revised *draft* Package Insert (four copies) and two sets of Final Printed vial labels, and shelf pack labels; the Appendix (Volume 2) contains ten [10] sets of Final Printed *draft* vial labels and shelf pack labels.

The Field Copy, as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

Baxter PPI trust that the Agency will find the response satisfactory. Should you have any questions, please do not hesitate to contact me, by telephone at 908/286-7215, or by fax at 908/286-7269, or David Ziering PhD, Associate Director - Regulatory CMC, by telephone at 908/286-7221.

Sincerely,

Priya Jambhekar

Priya Jambhekar
Director, Regulatory Affairs

*NW
1-2-01*

enc: Form 356h; Minor Amendment

BaxterVia Airborne overnight ExpressFood and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773Attention: Mr. Gary Buehler
Acting Director, Office of Generic Drugs [OGD]

April 28, 2000

ack for filing
S. Middleton
SOS (K) 5/26/00re: **Original ANDA - Milrinone Lactate Injection, USP;
1 mg/mL in 10 mL, 20 mL, 50 mL Vials**

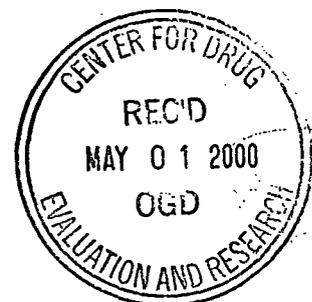
Dear Mr. Buehler:

According to 21 CFR 314.94, Baxter Pharmaceutical Products Inc. [BPPI] is submitting in duplicate an ANDA for Milrinone Lactate Injection, USP (milrinone). Similar to the listed drug, Primacor® (milrinone lactate) Injection, this ANDA contains the following presentations of milrinone:

- 1 mg/mL in 10 mL Vial
- 1 mg/mL in 20 mL Vial
- 1 mg/mL in 50 mL Vial

This submission is formatted in accordance with "Guidance for Industry: Organization of an Abbreviated New Drug Application and Abbreviated Antibiotic Application" (FDA/CDER, April 1997), and the ANDA sections are organized as follows:

ANDA Sections	Submission Volume
Cover Letter, Field Copy Documentation, Table of Contents.	1
1 - 7	1
8 - 11	2
12	3
12.3 <i>Sterility Assurance</i>	4
13 - 15	5
16	6
17 - 21	7
6 <i>Bio-equivalence review copy</i>	8
16 <i>Two extra sets of MVP</i>	9 & 10



Mr. Gary Buehler
April 28, 2000
Page 2

The archival copy is submitted in blue jackets, the Chemistry, Manufacturing, and Controls review copy (without Section 5 – Labeling) is bound in red, and the Bio-equivalence review copy (volume 8) is in an orange jacket. Two extra sets of the Methods Validation Package, volumes 9 and 10, are also included.

The Field Copy (volumes 1 through 7, without Section 5 - Labeling), as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office. Should you have any questions, please do not hesitate to contact me by telephone at 908/386-7215, or by facsimile at 908/286-7269.

Sincerely,



Priya Jambhekar
Director, Regulatory Affairs

enc: Form 356h; original ANDA

Baxter

July 27, 2000

Via Airborne overnight Express

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

ORIG AMENDMENT

AA

Attention: Mr. Gary Buehler
Acting Director, Office of Generic Drugs [OGD]

re: **ANDA 75-852 - Milrinone Lactate Injection, USP;**
1 mg/mL in 10 mL, 20 mL, 50 mL Vials

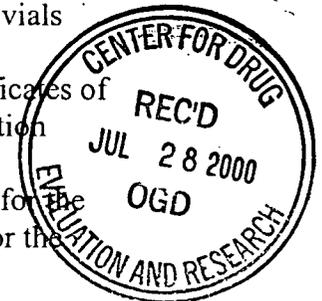
Correspondence to Pending ANDA: Tightening of Injection Specification

Dear Mr. Buehler:

According to 21 CFR 314.96, Baxter Pharmaceutical Products Inc. [Baxter PPI] is submitting, in duplicate, a correspondence to the above ANDA, #75-542, to provide for revised regulatory specifications for the injection to (1) tighten the limit for bacterial endotoxins from NMT EU/mg to NMT EU/mg , based on a re-evaluation of the FDA guidance, and (2) tighten the stability limit for total degradants from NMT $\%$ to NMT $\%$, based on the currently available stability data.

This submission contains the following revised/updated information organized in sections as per the original ANDA:

- Section 11 "Manufacturing and Processing Instructions": revised, master "Finished Product Specifications and Data Sheets" for the 10 mL, 20-mL, and 50-mL vials
- Section 12 "In-Process Controls": revised, executed "Finished Product Specifications and Data Sheets" for the 10 mL, 20-mL, and 50-mL vials
- Section 15 "Controls for the Finished Dosage Form: revised Certificates of Analysis for the ANDA batches and revised drug product specification
- Section 16 "Analytical Methods": revised Certificates of Analysis for the ANDA batches, revised drug product specification, and rationale for the specification revisions
- Section 17 "Stability": updated stability data report and marketed product stability testing plan revised to include all presentations in the program.



7/28/00
MPN-2

Mr. Gary Buehler – OGD

July 27, 2000

Page 2

Two additional copies of the Methods Validation Package, Section 16, are included. The Field Copy, as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office. Should you have any questions, please do not hesitate to contact me by telephone at 908/386-7215 or by facsimile at 908/286-7269.

Sincerely,



Priya Jambhekar
Director, Regulatory Affairs

enc: Form 356h

Baxter

June 14, 2000

Via Facsimile and Airborne overnight Express

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room – HFD-615, MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

NEW CORRESP
NC

Attention: Ms. Sandra Middleton,
Office of Generic Drugs [OGD]

re: **ANDA 75-852- Milrinone Lactate Injection, USP;**
1 mg/mL in 10 mL, 20 mL, 50 mL Vials

Correspondence to the Pending ANDA

Dear Ms. Middleton:

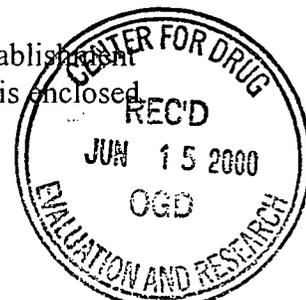
Reference is made to our telecon of this morning. As discussed, Baxter Pharmaceutical Products Inc. [Baxter PPI] is providing a written clarification of the names of the product release facilities included in Section 9, Description of the Manufacturing Facility (page 0227).

As indicated on page 0227, all release testing is performed by:

The Baxter PPI New Providence facility is not responsible for conducting any actual microbial or analytical testing of milrinone in support of product release. As an application holder, Baxter PPI reviews all of the completed paperwork, and releases the product for introduction into interstate commerce.

The Baxter Caribe facility has no involvement in any aspect of manufacturing, testing, or distribution of this product. The drug establishment number of this facility was inadvertently included under the Baxter PPI name.

We have revised page 0227 of the milrinone ANDA to remove the drug establishment number of our Puerto Rico facility, and a corrected replacement page 0227 is enclosed.



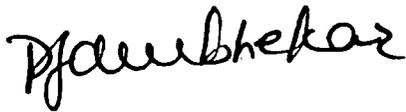
Ms. Saundra Middleton, OGD – HFD-615

June 14, 2000

Page 2

We apologize for any inconvenience caused. Please call me by telephone at 908/286-7215, or by facsimile at 908/286-7269, if I can be of further assistance.

Sincerely,

A handwritten signature in black ink, appearing to read "Priya Jambhekar". The signature is written in a cursive style with a large initial 'P'.

Priya Jambhekar

Director, Regulatory Affairs

enc: Form 356h
Replacement page 0227

Baxter

June 20, 2001

via Facsimile and Airborne overnight ExpressFood and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773Attention: Mr. Gary Buehler, Acting Director
Office of Generic Drugs

Desk copy: Ms. Bonnie McNeal, OGD Project Manager

N/A M
ORIG AMENDMENTre: **ANDA 75-852 - Milrinone Lactate Injection, USP**
1 mg/mL in 10 mL, 20 mL, 50 mL Vials, in 5% Dextrose
Second Telephone Amendment to the Pending ANDA

Dear Mr. Buehler:

Pursuant to the telephone discussion of June 19, 2001 between Ms. Bonnie McNeal, OGD and Priya Jambhekar, Baxter Healthcare Corporation, Anesthesia & Critical Care [formerly Baxter PPI], we are submitting, herein, a change in the drug substance specifications. The specification for residual solvent, toluene, has been revised from NMT % to NMT ppm; the methanol specification remains unchanged, although instead of being specified as NMT % it is now expressed as NMT ppm. The revised specification is enclosed for your review.

The Field Copy, as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

Should you have any questions or need further information please do not hesitate to contact me at 908/286-7215 or *via* fax at 908/286-7269. Many thanks, in advance, for your prompt review.

Sincerely,



Priya Jambhekar
Director, Regulatory Affairs



enc: Form 356h
Second Telephone Amendment

Baxter

Multi Duplt
PMB

June 12, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Acknowledged
MAI
P. Buehler
6/25/01

NEW CORRESP

NC
3-1

Attention: Mr. Gary Buehler, Acting Director
Office of Generic Drugs

re: **ANDA 75-852 - Milrinone Lactate Injection, USP**
1 mg/mL in 10 mL, 20 mL, 50 mL Vials, in 5% Dextrose

**General Correspondence: Name Change of Application Holder to
Baxter Healthcare Corporation**

Dear Mr. Buehler:

Reference is made to the above-mentioned application for Milrinone which was submitted on 4/28/00 by Baxter Pharmaceutical Products Inc. [Baxter PPI], a wholly-owned subsidiary of Baxter Healthcare Corporation [BHC]. On 12/31/00, Baxter PPI merged with BHC and its business and assets were assumed by BHC.

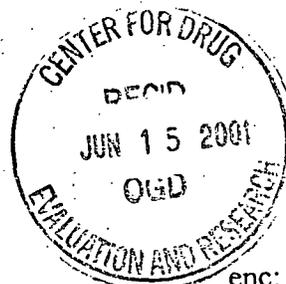
This change does not impact the product labeling, which is already in the name of BHC. There are no changes in the location or personnel. Please note that, in spite of the name change to Baxter Healthcare Corporation, our facility in New Providence, NJ, will retain administrative responsibility of the above-referenced application. Correspondence should be addressed as follows:

Priya Jambhekar
Director, Regulatory Affairs
Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence NJ 07974

Should you have any questions, please contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Priya Jambhekar



enc: Form FDA 356h

Baxter

May 16, 2001

via Facsimile and Airborne overnight Express

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

N/AM

DRUG AMENDMENT

Attention: Mr. Gary Buehler, Acting Director
Office of Generic Drugs

Desk copy: Ms. Bonnie McNeal, OGD Project Manager

re: **ANDA 75-852 - Milrinone Lactate Injection, USP**
1 mg/mL in 10 mL, 20 mL, 50 mL Vials, in 5% Dextrose
Telephone Amendment to the Pending ANDA

Dear Mr. Buehler:

Reference is made to the telephone request of April 24, 2001 from the Agency to Baxter Pharmaceutical Products [Baxter PPI], for an evaluation of a change in the specifications of the residual solvents, () present in the active ingredient milrinone lactate, to comply with the International Conference of Harmonization [ICH] guideline (ref. 62FR 67377, Dec 24, 1997, entitled "*Guidance on Impurities: Residual Solvents*"), copy enclosed.

According to the subject ICH guideline, () are considered Class 2 residual solvents. For such Class 2 solvents, maximum allowable limits can either be established by the "fixed" parts per million allowable amounts: () ppm for () and () ppm for () as stated in Option 1 or, if Option 1 cannot be met, the maximum limits can be established by the calculation of Permitted Daily Exposure [PDE] of the solvent based upon the calculated maximum daily dose of the drug product as stated in Option 2 (PDE values listed in the guideline are 30 mg for () and 8.9 mg for ()

The residual solvent specifications proposed by Baxter PPI based upon the drug substance manufacturer () specifications for milrinone lactate drug substance, () % for () and () % for () are within the allowable ICH limits based upon PDE limits (Option 2) as illustrated below. As can be seen, the maximum amounts of the () residual solvents that may be present in the finished product are significantly below the PDE limits of () mg and () mg for () respectively and, therefore, are in compliance with the ICH Guideline on Impurities, "*Residual Solvents*".



Residual Solvent [RS]	Baxter PPI & (NDS mfr.) limits	Permitted Daily Exposure [PDE] limits	Maximum Daily Exposure of RS based upon labeling ¹ (in 70 kg adult)	Maximum Daily Exposure of RS based upon labeling ¹ (in 120 kg adult)
	%)mg	0.166 mg ²	0.284 mg ³
	%)mg	0.415 mg ⁴	0.710 mg ⁵

NOTE: The other excipients in the formulation, dextrose, lactose, and sodium hydroxide, do not contain the residual solvents,

The Field Copy, as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

Should you have any questions or need further information please do not hesitate to contact Dr. David Ziering, Associate Director, CMC, by telephone at 908/286-7221, or me at 908/286-7215 or *via fax* at 908/286-7269.

Many thanks, in advance, for your prompt review.

Sincerely,



Priya Jambhekar
 Director, Regulatory Affairs

enc: Form 356h; Telephone Amendment

¹ Dosing and administration of milrinone lactate (1 mg /mL strength) recommended in the labeling (see Dosage and Administration of the Package Insert) is a combination of loading dose and maintenance dose expressed in milligrams per kilogram weight.

- In a 70 kg adult: Recommended loading dose = 3.5 mL or 3.5 mg. + the recommended maintenance dose range is 0.59 mg/kg to 1.13 mg/kg. A maximum recommended daily dose, therefore, would be 83 mgs $((3.5 + (1.13 \times 70) = 82.6 \text{ mg}))$.
- In a 120 kg adult (maximum weight listed in the labeling): recommended loading dose = 6.0 mL or 6.0 mgs + the recommended maintenance dose range is 0.59 mg/kg to 1.13 mg/kg. A maximum recommended daily dose therefore would be 142 mgs $((6.0 + (1.13 \times 120) = 141.6 \text{ mg}))$.

² 0.2% (maximum amount of toluene allowed) x 83 (maximum amount of milrinone administered per day in 70 kg adult) ÷ 100 = 0.166 mg

³ 0.2% (maximum amount of toluene allowed) x 142 (maximum amount of milrinone administered per day in 120 kg adult) ÷ 100 = 0.284 mg

⁴ 0.5% (maximum amount of toluene allowed) x 83 (maximum amount of milrinone administered per day in 70 kg adult) ÷ 100 = 0.415 mg

⁵ 0.5% (maximum amount of toluene allowed) x 142 (maximum amount of milrinone administered per day in 120 kg adult) ÷ 100 = 0.710 mg