CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75660

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-660** Date of Submission: **June 29, 1999**

Applicant's Name: **Bedford Laboratories**

Established Name: **Milrinone Lactate Injection, 1 mg (base)/mL, 10 mL and 20 mL vials**

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. The established name for this drug product is Milrinone Lactate Injection. Please revise throughout your labels and labeling where appropriate.

   b. Please revise your storage temperature recommendations throughout your labels and labeling as follows:

      Store at controlled room temperature 15° to 30°C (59° to 86°F) (see USP).

   c. Place an asterisk after the primary expression of strength (e.g. 10 mg/10 mL*) and immediately before the "Each mL contains ..." statement.

   d. We note that in parts of your application for your pH adjustment you have listed "lactic acid and/or sodium hydroxide" while on your carton labeling you have "lactic acid or sodium hydroxide". Please clarify.

2. CONTAINER 10 mL and 20 mL

   a. See GENERAL COMMENTS (a) through (c) above.

   b. Add the statement "Discard unused portion after initial use."

   c. Increase the prominence of the secondary expression of strength (1 mg/mL).

3. CARTON 10 x 10 mL and 10 x 20 mL

   See GENERAL COMMENTS and (c) under CONTAINER above.

4. INSERT

a. DESCRIPTION

i. "structural formula" rather than "structure"

ii. Second paragraph, first sentence - ... and a molecular formula ... ("a" rather than "an")

b. CLINICAL PHARMACOLOGY

i. Delete the sixth paragraph (A further ... subgroup.).

ii. Pharmacodynamics

A). Revise the first paragraph as follows:

In patients with heart failure due to depressed myocardial ... a prompt dose and plasma concentration related increase ... vascular resistance, which were accompanied by mild-to-moderate increases in heart rate. Additionally, there is no increased effect on myocardial oxygen consumption. In uncontrolled studies, hemodynamic improvement during intravenous therapy with milrinone ... symptomatic improvement, but the ability of milrinone to relieve symptoms has not been evaluated in controlled clinical trials. The great majority ...

B). Second paragraph - Delete the third sentence (The heart rate ... respectively).).

C). Third paragraph - Delete the second sentence (Patients have ... 5 days.).

c. INDICATIONS AND USAGE

Revise this section as follows:

Milrinone lactate injection is indicated for the short-term intravenous treatment of patients with acute decompensated heart failure. Patients receiving milrinone should be observed closely with appropriate electrocardiographic equipment. The facility for immediate treatment of potential cardiac events, which may include life threatening ventricular arrhythmias, must be available. The majority of experience with intravenous milrinone has been in patients receiving digoxin and diuretics. There is no experience in controlled trials with infusions of milrinone for periods exceeding 48 hours.

d. WARNINGS

Add a WARNINGS section with accompanying text (in bold print) to immediately follow the INDICATIONS AND USAGE section:

WARNINGS
Whether given orally or by continuous or intermittent intravenous infusion, milrinone has not been shown to be safe or effective in the longer (greater than 48 hours) treatment of patients with heart failure. In a multicenter trial of 1088 patients with Class III and IV heart failure, long-term oral treatment with milrinone was associated with no improvement in symptoms and an increased risk of hospitalization and death. In this study, patients with Class IV symptoms appeared to be at particular risk of life-threatening cardiovascular reactions. There is no evidence that milrinone given by long-term continuous or intermittent infusion does not carry a similar risk.

The use of milrinone both intravenously and orally has been associated with increased frequency of ventricular arrhythmias, including nonsustained ventricular tachycardia. Long-term oral use has been associated with an increased risk of sudden death. Hence, patients receiving milrinone should be observed closely with the use of continuous electrocardiographic monitoring to allow the prompt detection and management of ventricular arrhythmias.

e. PRECAUTIONS

Decrease the prominence of the subsection heading "USE IN ACUTE MYOCARDIAL INFARCTION".

f. DOSAGE AND ADMINISTRATION

Paragraph after "MAINTENANCE DOSE" chart - "milliliters" (spelling)

g. HOW SUPPLIED

i. See GENERAL COMMENTS (1)(b).

ii. Add the statement "Discard unused portion after initial use."

Please revise your container labels and carton and insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at

least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-660** Date of Submission: **September 12, 2000**

Applicant's Name: **Bedford Laboratories**

Established Name: **Milrinone Lactate Injection, 1 mg (base)/mL, 10 mL, 20 mL and 50 mL vials**

Labeling Deficiencies:

INSERT

ADVERSE REACTIONS

Other Effects - "Isolated ... received; and in the post-marketing experience, liver function test abnormalities have been reported."

Please revise your insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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/S/

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