

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75834

CHEMISTRY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II
Branch VIII
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 1
2. ANDA # 75-834
3. NAME AND ADDRESS OF APPLICANT
Baxter Healthcare Corporation
Attn: Ms. Marcia Marconi
Route 120 and Wilson Rd
Round Lake
IL 60073
4. LEGAL BASIS FOR SUBMISSION
The subject of this submission is Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container. The route of administration, dosage form, strength and volume are identical to the reference premixed drug, Primacor® (milrinone lactate) Injection described in NDA 20-343, held by Sanofi Pharmaceuticals, Inc. Patent Expiration Date: 02/02/01
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME N/A
7. NONPROPRIETARY NAME
Milrinone Lactate in 5% Dextrose
8. SUPPLEMENT PROVIDE:
N/A
9. AMENDMENTS AND OTHER DATES:

Firm:
Orig. Sub. 03/31/2000
Subject of this review

FDA:

Acknowledgement 05/30/2000
Bio Approval 06/22/2000
Labeling Deficiency letter 06/07/2000

10. PHARMACOLOGICAL CATEGORY

Vasodilator

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF number	DMF type	DMF holder

13. DOSAGE FORM

Injection

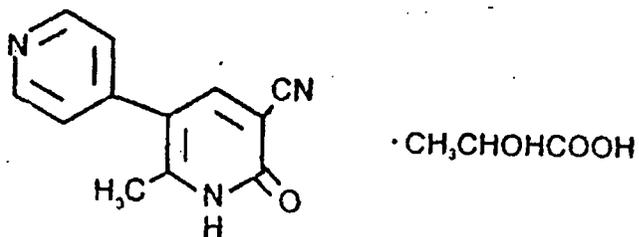
14. POTENCY

0.2 mg/mL

14. CHEMICAL NAME AND STRUCTURE

Milrinone. [3,4'-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-. C₁₂H₉N₃O. 211.22. 78415-72-2. Cardiotonic. USAN 93, page 413.

Chemical Structure of milrinone lactate:



Molecular Formula of milrinone: C₁₂H₉N₃O

Molecular Weight of milrinone: 211.2

16. RECORDS AND REPORTS

N/A

17. COMMENTS

a. EER status: Pending

EER, requested by Tim Ames on May 30, 2000.

b. Method Validation status: Pending, Non-Compndial.
Required since both drug substance and finished product are not official USP items.

c. Bio-review status: Satisfactory

The waiver of in vivo bioavailability was granted and satisfactory per Dhariwal, reviewed on 6-22-2000.

d. Micro-review status: pending

e. Labeling review status:
Not Satisfactory as per A. Vezza, reviewed on 6-07-2000.

f. DMF () Not Adequate

DMF# () was reviewed by Mouna P. Selvam and found not satisfactory on August 21, 2000

DMFs () satisfactory, M. Selvam, 9/25/00 & 10/20/00.

18. CONCLUSIONS AND RECOMMENDATIONS:

The application is not Approved - Major

19. REVIEWER:

DATE COMPLETED:

Mouna P.Selvam, Ph.D., 10/26/2000

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Chem Review #1

NOV 17 2000

38. Chemistry Comments to be provided to the Applicant:

ANDA: 75-834 APPLICANT: Baxter Health Care Corporation

DRUG PRODUCT: Milrinone Lactate Injection 0.2 mg/mL in 5%
Dextrose

The deficiencies presented below represent Major deficiencies.

A. Chemistry Deficiencies:

1. The component statement (page 54) provides for the use of () whereas the actual material used in the manufacture of the drug product is Dextrose Hydrus. Please revise the component statement and resubmit.
2. The limit for the ID () test is not specific. A specific limit should be included. Please revise and resubmit.
3. Please include tests, methods and limits for Residual Solvents, Color of solution, Organic volatile impurities and assay () basis) in the drug substance release certificate. Data should be submitted for a test batch.
4. The limit for total impurities is high and is not supported by your data or that of the () DS supplier. Please tighten the limit for total impurities.
5. Regarding inactive ingredient testing, we acknowledge the submitted certificates of analysis for the inactives, however, we request that you provide a list of the current compendial tests, methods and limits used in the testing of each inactive. Also, please identify which of these tests are routinely performed for batch release.
6. The description of the manufacturing process

7. The product formulation (page 84 and 97) assumes that the 'as is' potency of milrinone is always _____; but the equation for calculating the actual amount is provided for 100% potency. The amount of milrinone in the formula table should include the amount of milrinone at 100% potency and the equation should be used to calculate the required amount of milrinone. Please revise and resubmit.
 8. We request that you specify in the batch record the maximum bulk solution holding time for pre and post filtration.
 9. We request you to provide data comparing your Drug Product impurity/degradant profile with the innovator's impurity/degradant profile.
 10. Please include a limit for individual known and unknown impurities/degradants at release and stability.
 11. The limit for total impurities/degradants is not justified by data. Please include a tighter limit.
 12. The forced degradation study should be repeated on samples of the drug product solution in order to evaluate interference from potential excipient interaction. Please submit results.
- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. DMF _____ has been reviewed and found deficient. This ANDA cannot be approved until these deficiencies have been resolved.
 2. Methods validation will be performed on the drug substance and drug product by the FDA field Laboratory.
 3. A satisfactory compliance evaluation for the Firms referenced in the ANDA is required for approval. The Establishment Evaluation Request (EER) is pending.

4. Microbiology review for this application is pending.

Sincerely yours,

(/S/)

sf

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II
Branch VIII
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-834

3. NAME AND ADDRESS OF APPLICANT

Baxter Healthcare Corporation
Attn: Ms. Marcia Marconi
Route 120 and Wilson Rd
Round Lake
IL 60073

4. LEGAL BASIS FOR SUBMISSION

The subject of this submission is Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container. The route of administration, dosage form, strength and volume are identical to the reference premixed drug, Primacor® (milrinone lactate) Injection described in NDA 20-343, held by Sanofi Pharmaceuticals, Inc. Patent Expiration Date: 02/02/01

5. SUPPLEMENT (s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME

Milrinone Lactate in 5% Dextrose in PL 2408 Plastic Container

8. SUPPLEMENT PROVIDE:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

Orig. Sub.

03/31/2000

Amendment

12/21/2000 Subject of this review

FDA:

Acknowledgement	05/30/2000
Bio Approval	06/22/2000
Labeling Review letter	06/07/2000
Labeling Review letter	01/22/2001

10. **PHARMACOLOGICAL CATEGORY**
Vasodilator

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**

DMF#	DMF type	DMF holder

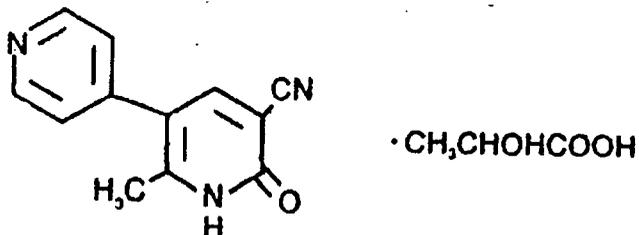
13. **DOSAGE FORM**
Injection

14. **POTENCY**
0.2 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**

Milrinone. [3,4'-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-. C₁₂H₉N₃O. 211.22. 78415-72-2. Cardiotonic. USAN 93, page 413.

Chemical Structure of milrinone lactate:



Molecular Formula of milrinone: C₁₂H₉N₃O

Molecular Weight of milrinone: 211.2

16. RECORDS AND REPORTS

N/A

17. COMMENTS

- a. EER status: Pending for Gensia
- b. Method Validation status: Pending, Non-Compndial.
Required since both drug substance and finished products are not official USP items.
- c. Bio-review status: Satisfactory
The waiver of in vivo bioavailability was granted and satisfactory per Dhariwal, reviewed on 6-22-2000.
- d. Micro-review status: Satisfactory, 1/9/01
- e. Labeling review status:
Not Satisfactory as per A. Vezza, reviewed on 01-22-2001.
- f. DMF () Not Adequate
DMF# _____ was reviewed by Mouna P. Selvam and found not satisfactory on January 17, 2001

18. CONCLUSIONS AND RECOMMENDATIONS:

The application is not Approvable - Minor

19. REVIEWER: DATE COMPLETED:

Mouna P. Selvam, Ph.D., 02/09/2001

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Chem-Review #2

FEB 20 2001

38. Chemistry Comments to be provided to the Applicant:

ANDA: 75-834 APPLICANT: Baxter Health Care Corporation

DRUG PRODUCT: Milrinone Lactate Injection in 5% Dextrose Injection (200 mcg base/mL) 100 mL and 200 mL

The deficiencies presented below represent Minor deficiencies.

A. Chemistry Deficiencies:

1. Your response to our comment #1 is not satisfactory. The component composition statement is used for calculating the batch composition. The labeling also reflects what is in this statement. In order to address your concern we suggest that you include the following in the composition statement: (as Dextrose Hydrous). Please revise and resubmit.
2. Your response to our comment #2 is not satisfactory. The proposed deviation in retention time for the sample from a house standard is large and is not justified. Please provide for a tighter limit.
3. Your response to our comment #3 is not satisfactory. Please include a limit for the drug substance assay test that is consistent with the drug substance supplier.
4. Your response to our comment #4 is not satisfactory. You have not addressed our comment regarding the impurity specification in the drug substance Milrinone. Please do so.
5. Your response to our comment #6 is not satisfactory. Please revise the manufacturing record and delete these potency adjustments completely.
6. Please include the holding time, as provided in the covering letter, in the batch record.
7. The proposed specifications for the drug product at release and stability are not justified for the known

impurities. The limit for unknown is not acceptable. We believe that at this level the unknown impurities should be characterized. The safety issues pertaining to these impurities at the proposed levels are not known. Please propose more reasonable limits based on available data and the nature of these impurities.

8. The chromatograms of the forced degradation study, presented in Attachment 10 (pages 56-59), represent only the light exposure stress studies and blanks. Please submit data including peak purity, (HPLC) chromatograms and tabulated percent degradation for samples stressed under acid, base, oxidative, and heat conditions.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. DMF has been reviewed and found deficient. This ANDA cannot be approved until these deficiencies have been resolved.
2. Methods validation is pending.
3. A satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval. The Establishment Evaluation Request (EER) is pending.

Sincerely yours,

fd */S/*
Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II
Branch VIII
Abbreviated New Drug Application Review

1. **CHEMISTRY REVIEW NO. 3**

2. **ANDA # 75-834**

3. **NAME AND ADDRESS OF APPLICANT**

Baxter Healthcare Corporation
Attn: Ms. Marcia Marconi
Route 120 and Wilson Rd
Round Lake
IL 60073

4. **LEGAL BASIS FOR SUBMISSION**

The subject of this submission is Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container. The route of administration, dosage form, strength and volume are identical to the reference premixed drug, Primacor® (milrinone lactate) Injection described in NDA 20-343, held by Sanofi Pharmaceuticals, Inc. Patent Expiration Date: 02/02/01

5. **SUPPLEMENT (s)** N/A

6. **PROPRIETARY NAME** N/A

7. **NONPROPRIETARY NAME**

Milrinone Lactate in 5% Dextrose in PL 2408 Plastic Container

8. **SUPPLEMENT PROVIDE:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

Firm:

Orig. Sub.	03/31/2000
Amendment	12/21/2000
FAX Amendment	06/13/2001

Amendment 07/25/2001 &
Fax Amendment 08/30/2001 &
Fax Amendment 09/12/2001

Subject of this review

FDA:

Acknowledgement 05/30/2000
Bio Approval 06/22/2000
Labeling Review letter 06/07/2000
Labeling Review letter 01/22/2001
Teleconference 06/06/2001
Teleconference 06/18/2001
Teleconference 07/09/2001
Labeling Review letter 08/23/2001
Telecon 08/29/2001
Telecon 09/07/2001

10. PHARMACOLOGICAL CATEGORY

Vasodilator

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF#	DMF type	DMF holder

13. DOSAGE FORM

Injection

14. POTENCY

0.2 mg/mL

Telecon 08/29/2001
Telecon 09/07/2001

17. COMMENTS:

- a. EER status: Acceptable as of April 16, 2001
- b. Method Validation status: Lab has received the samples from the Firm.
- c. Bio-review status: Satisfactory
The waiver of in vivo bioavailability was granted and satisfactory per Dhariwal, reviewed on 6-22-2000.
- d. Micro-review status: Satisfactory, 1/9/01
- e. Labeling review status: Satisfactory, 08/23/2001
- f. DMF Adequate
Reviewed by Mouna P. Selvam, 04/23/2001.

18. CONCLUSIONS AND RECOMMENDATIONS:

The application is Approved.

19. REVIEWER: DATE COMPLETED:

Mouna P.Selvam, Ph.D., 09/13/2001

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Chem Review #3



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II
Branch VIII
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 4
 2. ANDA # 75-834
 3. NAME AND ADDRESS OF APPLICANT
Baxter Healthcare Corporation
Attn: Ms. Marcia Marconi
Route 120 and Wilson Rd
Round Lake, IL 60073
 4. LEGAL BASIS FOR SUBMISSION
The subject of this submission is Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container. The route of administration, dosage form, strength and volume are identical to the reference premixed drug, Primacor® (milrinone lactate) Injection described in NDA 20-343, held by Sanofi Pharmaceuticals, Inc. The current expiration of Marketing Exclusivity for the RLD Primacor in 5.0% Dextrose Inj. by Sanofi-Synthelabo, Inc is 05/26/02.
 5. SUPPLEMENT (s) N/A
 6. PROPRIETARY NAME N/A
 7. NONPROPRIETARY NAME
Milrinone Lactate in 5% Dextrose in PL 2408 Plastic Container
 8. SUPPLEMENT PROVIDE:
N/A
 9. AMENDMENTS AND OTHER DATES:
- Firm:
- | | |
|------------|------------|
| Orig. Sub. | 03/31/2000 |
| Amendment | 12/21/2000 |

FAX Amendment	06/13/2001
Amendment	07/25/2001
Fax Amendment	08/30/2001
Fax Amendment	09/12/2001
Minor Amendment	03/01/2002
<i>Telephone amendment</i>	Subject of this review 5/22/2002. (SMS)

FDA:

Acknowledgement	05/30/2000
Bio Approval	06/22/2000
Labeling Review letter	06/07/2000
Labeling Review letter	01/22/2001
Teleconference	06/06/2001
Teleconference	06/18/2001
Teleconference	07/09/2001
Labeling Review letter	08/23/2001
Telecon	08/29/2001
Telecon	09/07/2001
Tentative Approval	10/30/2001

10. PHARMACOLOGICAL CATEGORY

Vasodilator

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF#	DMF type	DMF holder

13. DOSAGE FORM

Injection

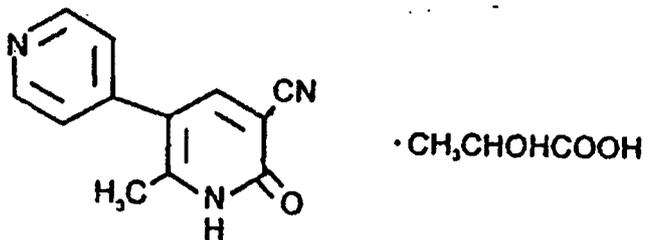
14. POTENCY

0.2 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Milrinone. [3,4'-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-. $C_{12}H_9N_3O$. 211.22. 78415-72-2. Cardiotonic. USAN 93, page 413.

Chemical Structure of milrinone lactate:



Molecular Formula of milrinone: $C_{12}H_9N_3O$

Molecular Weight of milrinone: 211.2

16. RECORDS AND REPORTS:

Firm:

Orig. Sub.	03/31/2000
Amendment	12/21/2000
FAX Amendment	06/13/2001
Amendment	07/25/2001
Fax Amendment	08/30/2001
Fax Amendment	09/12/2001
Minor Amendment	03/01/2002

FDA:

Acknowledgement	05/30/2000
Bio Approval	06/22/2000
Labeling Review letter	06/07/2000
Labeling Review letter	01/22/2001
Teleconference	06/06/2001

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Chem Review #4