# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75852**

## CHEMISTRY REVIEW(S)

# ANDA APPROVAL SUMMARY

**ANDA:** 75-852

**DRUG PRODUCT:** Milrinone Lactate in 5% Dextrose

**FIRM:** Baxter Pharmaceuticals Products Inc.,(BPP)

**DOSAGE FORM:** Injection

**STRENGTH:** 1.0 mg/mL, 10 mL, 20 mL and 50 mL Vials

**CGMP STATMENT/EER UPDATE STATUS:**

Overall recommendation - Acceptable as of 03/08/2001

**BIO STUDY:** Bio-waiver request - Acceptable on 06/26/2000, K. Dhariwal

**VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):**

Non-USP Item.
As of 04/23/2001, Methods Validation at the District Lab is Pending.

**STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:**

Accelerated and CRT stability data satisfactory for 10 mL Batch #99H217; 20 mL Batch #99H216 and 50 mL Batch #99N210. The Container Closure is the same as that described in the container closure section.

**LABELING:** Satisfactory, A. Vezza, 04/02/2001

**STERILIZATION VALIDATION (IF APPLICABLE):**
Satisfactory, 01/17/2001

**SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):**

DMF for Milrinone is satisfactory on 06/26/01, reviewed by Mouna Selvam.
10 mL Batch #99H217, 20 mL Batch #99H216,
50 mL Batch #99N210,

**SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):**

See above for batch size. Stability protocol, commitment and expiration date of 24 months (tentative) satisfactory.

**PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:**

Proposed batch size is L [10 mL fill] (compared with L executed batch size); L [20 mL fill] (compared with L executed batch size); L [50 mL fill] (compared with L executed batch size) and use same /similar equipment and in-process controls for proposed batch as the executed batch.

/S/

**CHEMIST:** Mouna Selvam, Ph.D. **DATE:** 06/25/01

**SUPERVISOR:** U.V. Venkataram, Ph.D., **DATE:** ~~04/23/01~~ 07/05/01

FT BY:

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 # 75-852

3. NAME AND ADDRESS OF APPLICANT
Baxter Pharmaceuticals Products Inc.
Attn: Ms. Priya Jambhekar
95 Spring St.
New Providence
NJ-07974-1143

4. LEGAL BASIS FOR SUBMISSION
The subject of this submission is Milrinone Lactate in 5% Dextrose Injection. The route of administration, dosage form, strength and volume are identical to the reference premixed drug, Primacor® (milrinone lactate) Injection described in NDA 19-436, held by Sanofi Pharmaceuticals, Inc. Patent Expiration Date: 11/26/2001.

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. | 04/28/00 Subject of this review |
| Orig. Amendment | 07/27/00 Subject of this review |

FDA:

| | |
|---|---|
| Acknowledgement | 06/02/2000 |
| Bio Waiver Approval | 06/26/2000 |
| Labeling Deficiency letter | 08/22/2000 |

10. **PHARMACOLOGICAL CATEGORY**
Vasodilator

11. **Rx or OTC**
Rx

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

| DMF number | DMF type | DMF holder |
|---|---|---|
| | Milrinone Drug Substance | |
| | Stopper | |
| | Glass | |
| | Glass | |
| | Glass | |

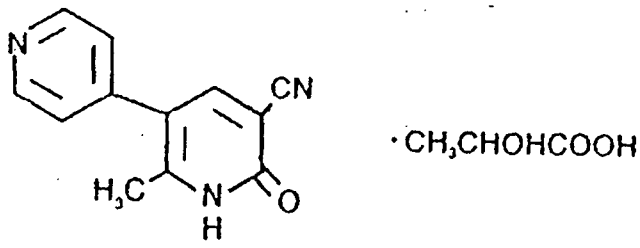
13. **DOSAGE FORM**
Injection

14. **POTENCY**
1.0 mg/mL (10 mL, 20 mL and 50 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
N/A

17. COMMENTS

a. EER status: Acceptable for all Facilities except Gensia Sicor, which is pending.
EER, requested by Middleton on June 19, 2000.

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

c. Bio-review status: Satisfactory

The waiver of in vivo bio-availability was granted and satisfactory per Dhariwal, reviewed on 6-26-2000.

d. Micro-review status: pending

e. Labeling review status:
Not Satisfactory as per A. Vezza, reviewed on 8-22-2000.

f. DMF Not Adequate
DMF# was reviewed by Mouna P. Selvam and found not satisfactory on October 24, 2000

18. CONCLUSIONS AND RECOMMENDATIONS:
The application is not Approved - Major

19. REVIEWER: DATE COMPLETED:
Mouna P.Selvam, Ph.D., 11/06/2000

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Chem Review #1

NOV 17 2000

**38. Chemistry Comments to be provided to the Applicant:**

ANDA: 75-852 APPLICANT: Baxter Pharmaceutical Products Inc.,

DRUG PRODUCT: Milrinone Lactate Injection 1.0 mg/mL in 5% Dextrose

The deficiencies presented below represent Minor deficiencies.

**Chemistry Deficiencies:**

1. The limit for the Identification ( ) test is not specific. A specific limit should be included. Please revise and resubmit.

2. Please include tests, methods and limits for Residual Solvents, Color of solution, Organic volatile impurities and assay (anhydrous basis) in the drug substance release certificate. Data should be submitted for a test batch.

3. 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.

4. The description of the manufacturing process includes

   Please revise the manufacturing process

5. We request that you specify in the batch record the maximum bulk solution holding time for pre and post filtration.

6. We request you to provide data comparing your Drug Product impurity/degradant profile with the innovator's impurity/degradant profile.

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 for {Gensia Sicor}.

4. The microbiology review for this application is pending.

Sincerely yours,

/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. 2

2. ANDA # 75-852

3. NAME AND ADDRESS OF APPLICANT
Baxter Pharmaceuticals Products Inc.
Attn: Ms. Priya Jambhekar
95 Spring St.
New Providence
NJ-07974-1143

4. LEGAL BASIS FOR SUBMISSION
The subject of this submission is Milrinone Lactate in 5% Dextrose Injection. The route of administration, dosage form, strength and volume are identical to the reference premixed drug, Primacor® (milrinone lactate) Injection described in NDA 19-436, held by Sanofi Pharmaceuticals, Inc. Patent Expiration Date: 11/26/2001.

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. | 04/28/00 | |
| Orig. Amendment | 07/27/00 | |
| Minor Amendment | 12/19/00 | Subject of this review |

**FDA:**

| | |
|---|---|
| Acknowledgement | 06/02/2000 |
| Bio Waiver Approval | 06/26/2000 |
| Labeling Review | 08/22/2000 |
| Labeling Review | 01/04/2001 |

**10. PHARMACOLOGICAL CATEGORY**

Vasodilator

**11. Rx or OTC**

Rx

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

| DMF# | DMF type | DMF holder |
|---|---|---|
| | Milrinone Drug Substance | |
| | Stopper | |
| | Glass | |
| | Glass | |
| | Glass | |

**13. DOSAGE FORM**

Injection

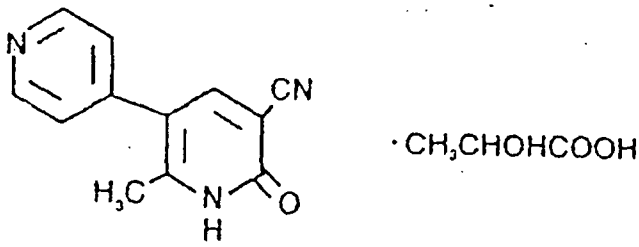
**14. POTENCY**

1.0 mg/mL (10 mL, 20 mL and 50 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**
N/A

17. **COMMENTS**

a. EER status: Pending for Gensia

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

c. Bio-review status: Satisfactory
The waiver of in vivo bio-availability was granted and satisfactory per Dhariwal, reviewed on 6-26-2000.

d. Micro-review status: Satisfactory, 1/17/01

e. Labeling review status:
Not Satisfactory as per A. Vezza, reviewed on 01-04-2001.

f. DMF Inadequate
DMF# was reviewed by Mouna P. Selvam and found inadequate on January 17, 2001

18. **CONCLUSIONS AND RECOMMENDATIONS:**
The application is not approvable - Minor

19. **REVIEWER:** **DATE COMPLETED:**
Mouna P.Selvam, Ph.D., 02/12/2001

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Chem Review #2

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 # 75-852

3. NAME AND ADDRESS OF APPLICANT
Baxter Pharmaceuticals Products Inc.
Attn: Ms. Priya Jambhekar
95 Spring St.
New Providence
NJ-07974-1143

4. LEGAL BASIS FOR SUBMISSION
The subject of this submission is Milrinone Lactate in 5% Dextrose Injection. The route of administration, dosage form, strength and volume are identical to the reference premixed drug, Primacor® (milrinone lactate) Injection described in NDA 19-436, held by Sanofi Pharmaceuticals, Inc. Patent Expiration Date: 11/26/2001.

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. | 04/28/00 |
| Orig. Amendment | 07/27/00 |
| Minor Amendment | 12/19/00 |

Minor Amendment 03/23/01

Tel Amendment 05/16/2001
Tel Amendment 06/20/2001

**Subject of this review**

**FDA:**

| | |
|---|---|
| Acknowledgement | 06/02/2000 |
| Bio Waiver Approval | 06/26/2000 |
| Labeling Review | 08/22/2000 |
| Labeling Review | 01/04/2001 |
| Labeling Approval | 04/02/2001 |
| Telecon | 04/24/2001 |
| Telecon | 06/19/2001 |

**10. PHARMACOLOGICAL CATEGORY**

Vasodilator

**11. Rx or OTC**

Rx

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

| DMF# | DMF type | DMF holder |
|---|---|---|
| | Milrinone Drug Substance | |
| | Stopper | |
| | Glass | |
| | Glass | |
| | | |

**13. DOSAGE FORM**

Injection

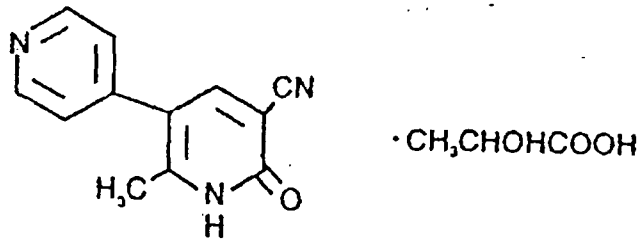
**14. POTENCY**

1.0 mg/mL (10 mL, 20 mL and 50 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. | 04/28/2000 |
| Orig. Amendment | 07/27/2000 |
| Minor Amendment | 12/19/2000 |
| Minor Amendment | 03/23/2001 |
| Tel Amendment | 05/16/2001 |
| Tel Amendment | 06/20/2001 |

**FDA:**

| | |
|---|---|
| Acknowledgement | 06/02/2000 |
| Bio Waiver Approval | 06/26/2000 |
| Labeling Review | 08/22/2000 |
| Labeling Review | 01/04/2001 |
| Labeling Approval | 04/02/2001 |
| Telecon | 04/24/2001 |
| Telecon | 06/19/2001 |

17. **COMMENTS**

a. EER status: Acceptable for all Facilities as of 03/08/2001

b. Method Validation status: Pending (called the District Lab on 04/23/01), Non-Compendial.

Required since both drug substance and drug product were not official USP items.

c. Bio-review status: Satisfactory
The waiver of in vivo bio-availability was granted and satisfactory per Dhariwal, reviewed on 6-26-2000.

d. Micro-review status: Satisfactory, 1/17/01

e. Labeling review status:
Satisfactory as per A. Vezza, reviewed on 04-02-2001.

f. DMF Adequate
DMF# was reviewed by Mouna P. Selvam and found Adequate on April 10, 2001.

The DMF updated the residual solvent procedure in the recent Amendment. The specification was tightened to ppm, while the remained constant at ppm, which is acceptable at this time.

Baxter, the drug product manufacturer also submitted the revised drug substance specifications. The specification for residual solvent, has been revised from NMT % to ppm and the specification is expressed as NMT ppm.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
The application is Approved

19. **REVIEWER:** **DATE COMPLETED:**
Mouna P.Selvam, Ph.D., 06/25/2001

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Chem Review #3

1. **CHEMISTRY REVIEW: NO. 4**

2. **ANDA: # 75-852**

3. **NAME AND ADDRESS OF APPLICANT:**
Baxter Pharmaceuticals Products Inc.
Attn: Ms. Priya Jambhekar
95 Spring St.
New Providence
NJ-07974-1143

4. **LEGAL BASIS FOR SUBMISSION:**
The subject of this submission is Milrinone Lactate in 5% Dextrose Injection. The route of administration, dosage form, strength and volume are identical to the reference premixed drug, Primacor® (milrinone lactate) Injection described in NDA 19-436, held by Sanofi-Synthelabo, Inc. Patent Expiration Date: 5/26/2002.

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. | 04/28/00 |
| Orig. Amendment | 07/27/00 |
| Minor Amendment | 12/19/00 |
| | |
| Minor Amendment | 03/23/01 |
| Tel Amendment | 05/16/2001 |
| Tel Amendment | 06/20/2001 |

Minor Amendment 04/05/2002

**Subject of this review**

**FDA:**

| | |
|---|---|
| Acknowledgement | 06/02/2000 |
| Bio Waiver Approval | 06/26/2000 |
| Labeling Review | 08/22/2000 |
| Labeling Review | 01/04/2001 |
| Labeling Approval | 04/02/2001 |
| Telecon | 04/24/2001 |
| Telecon | 06/19/2001 |
| Tentative Approval | 08/02/2001 |
| Labeling Approval | 04/19/2002 |

**10. PHARMACOLOGICAL CATEGORY:**

Vasodilator

**11. Rx or OTC:**

Rx

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

| DMF# | DMF type | DMF holder |
|---|---|---|
| | Milrinone Drug Substance | |
| | Stopper | |
| | Glass | |
| | Glass | |
| | Glass | |

**13. DOSAGE FORM:**

Injection

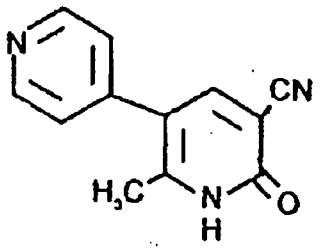
**14. POTENCY :**

**1.0mg/mL (10 mL, 20 mL and 50 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:**




·CH3CHOHCOOH

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

**Molecular Weight of milrinone: 211.2**

## 16. RECORDS AND REPORTS

**Firm:**

| | |
|---|---|
| Orig. Sub. | 04/28/2000 |
| Orig. Amendment | 07/27/2000 |
| Minor Amendment | 12/19/2000 |
| Minor Amendment | 03/23/2001 |
| Tel Amendment | 05/16/2001 |
| Tel Amendment | 06/20/2001 |
| Minor Amendment | 04/04/2002 |

**FDA:**

| | |
|---|---|
| Acknowledgement | 06/02/2000 |
| Bio Waiver Approval | 06/26/2000 |
| Labeling Review | 08/22/2000 |
| Labeling Review | 01/04/2001 |
| Labeling Approval | 04/02/2001 |
| Telecon | 04/24/2001 |
| Telecon | 06/19/2001 |
| Tentative Approval | 08/02/2001 |
| Labeling Approval | 04/19/2002 |

## 17. COMMENTS

a. EER status: Acceptable for all Facilities as of 03/08/2001

b. Method Validation status: Satisfactory

c. Bio-review status: Satisfactory
The waiver of in vivo bio-availability was granted and satisfactory per Dhariwal, reviewed on 6-26-2000.

d. Micro-review status: Satisfactory, 1/17/01

e. Labeling review status:
Satisfactory as per A. Vezza, reviewed on 04-19-2002.

f. DMF( ) is Adequate
DMF# was reviewed by Mouna P. Selvam and found adequate on March 27, 2002.

The DMF Holder updated the residual solvent procedure in the recent Amendment. The specification was tightened to ppm, while the remained constant at ppm, which is acceptable at this time.

Baxter, the drug product manufacturer also submitted the revised drug substance specifications. The specification for residual solvent, has been revised from NMT % to ppm and the specification is expressed as NMT ppm.

**18. CONCLUSIONS AND RECOMMENDATIONS:**
The application is ready for Full Approval

**19. REVIEWER:** Mouna P.Selvam, Ph.D.,

**DATE COMPLETED:** 05/21/2002

**38. Chemistry Comments to be provided to the Applicant:**

ANDA: 75-852 APPLICANT: Baxter Pharmaceutical Products, Inc.

DRUG PRODUCT: Milrinone Lactate Injection 1 mg(base)/mL in 10 mL, 20 mL, and 50 mL vials

The deficiencies presented below represent Minor deficiencies.

A. Chemistry Deficiencies:

1. The component composition statement should be revised to include exact quantitative amounts of the components. Also, please replace USP with Dextrose Anhydrous USP (as Dextrose Hydrous). Please revise and resubmit.

2. Please include an additional ID test such as retention time for the DS release testing.

3. The calculations shown on pages 3 and 4 of the manufacturing record (pages 253 and 254 of the original submission) for calculating the amount of ingredient are not clear. It is not clear whether this calculation pertains to that of milrinone or some other ingredient. The ingredient should be specified on each page. Page 3 provides calculations based on g/L of the ingredient whereas page 4 is based on g/L. Please explain and revise the batch record appropriately.

4. Your response to our comments (page#3 and 32) are not satisfactory. The limits for Other Individual Degradation Products and Total Degradation Products at shelf-life are high. Note that the Other Individual Degradation Products at the proposed shelf-life limits may need to be identified. The safety issues pertaining to these degradants are not known. Also, the data submitted does not support these limits. Please revise and resubmit.

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

1. DMF [redacted] has been found to be inadequate. The deficiencies have been communicated to the DMF holder.

2. Methods validation will be performed on the drug substance and drug product by the FDA field Laboratory and it 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 for [redacted] the drug product manufacturer.

Sincerely yours,

/S/

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