

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**40266**

**MICROBIOLOGY REVIEW**

OFFICE OF GENERIC DRUGS

Microbiologists Review #1

June 18, 1998

- A. 1. ANDA: **40-266**
- APPLICANT: Bigmar Inc.  
9711 Sportsman Club Road  
Johnstown, Ohio 43031-1941
2. PRODUCT NAME: **Methotrexate for Injection, USP**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:  
Lyophilized Powder, 1 gram/bottle. Reconstitute with a sterile, preservative free, medium to a concentration of 50 mg/mL for IV, IA, IM and IT injection. Free Single Dose Vials.
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: anti neoplastic
- B. 1. DATE OF INITIAL SUBMISSION: **July 31, 1997. Subject of this Review.**
2. DATE OF AMENDMENT:  
**September 17, 1997. Subject of this Review.**  
**December 20, 1997. Subject of this review.**  
**February 19, 1998. Subject of this Review.**  
**May 29, 1998. Subject of this Review.**  
**June 11, 1998. Subject of this Review**
3. RELATED DOCUMENTS: DMFs not reviewed. 40-263 preserved multi dose vials and 40-265 single dose vials.
4. ASSIGNED FOR REVIEW: June 12, 1998.
- C. REMARKS: A justification for processing is provided in the December 20, 1997 Amendment. Increases in impurities were seen after 121°C for 15 minutes. The May 29, 1998 Amendment contains Microbiology responses to concerns raised in the review of ANDA 40-258 (Leucovorin) by this reviewer. These responses have been applied to the appropriate questions in this review.
- D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in and "Draft of Letter to Applicant".

*IS/* *6/22/98*

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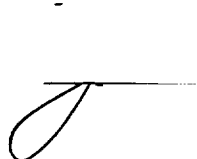
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*Microbiologist's Review #1*

OFFICE OF GENERIC DRUGS  
Microbiologists Review #2  
October 16, 1998

- A. 1. ANDA: **40-266**
- APPLICANT: Bigmar Inc.  
9711 Sportsman Club Road  
Johnstown, Ohio 43031-1941
2. PRODUCT NAME: **Methotrexate for Injection, USP**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:  
Lyophilized Powder, 1 gram/bottle. Reconstitute with a sterile, preservative free, medium to a concentration of 50 mg/mL for IV, IA, IM and IT injection. Free Single Dose Vials.
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: anti neoplastic
- B. 1. DATE OF INITIAL SUBMISSION: July 31, 1997.
2. DATE OF AMENDMENT:  
September 17, 1997.  
December 20, 1997.  
February 19, 1998.  
May 29, 1998.  
June 11, 1998.  
**September 18, 1998. Subject of this Review**
3. RELATED DOCUMENTS: DMFs not reviewed. 40-263 preserved multi dose vials and 40-265 single dose vials.
4. ASSIGNED FOR REVIEW: October 15, 1998.
- C. REMARKS: The same issues as provided for 40-263.
- D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in \_\_\_\_\_ and \_\_\_\_\_  
Draft of Letter to Applicant".

 **ISI**  
James L. McVey 10/16/98

initialed by R. Patel 10/16/98

cc:

Original ANDA  
Duplicate ANDA  
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drafted by: J. McVey 40266na2.m

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*micro Review # 2*

OFFICE OF GENERIC DRUGS  
Microbiologists Review #3  
December 18, 1998

- A. 1. ANDA: **40-266**  
APPLICANT: Bigmar Inc.  
9711 Sportsman Club Road  
Johnstown, Ohio 43031-1941
2. PRODUCT NAME: **Methotrexate for Injection, USP**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:  
Lyophilized Powder, 1 gram/bottle. Reconstitute with a sterile, preservative free, medium to a concentration of 50 mg/mL for IV, IA, IM and IT injection. Free Single Dose Vials.
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: anti neoplastic
- B. 1. DATE OF INITIAL SUBMISSION: July 31, 1997.
2. DATE OF AMENDMENT:  
September 17, 1997.  
December 20, 1997.  
February 19, 1998.  
May 29, 1998.  
June 11, 1998.  
September 18, 1998.  
**November 20, 1998. Subject of this Review**
3. RELATED DOCUMENTS: DMFs not reviewed. 40-263 preserved multi dose vials and 40-265 single dose vials.
4. ASSIGNED FOR REVIEW: December 18, 1998.
- C. REMARKS: The same issues as provided for 40-263. **A phone call should be made to assure that the remaining deficiencies are understood.**
- D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in \_\_\_\_\_ and \_\_\_\_\_

Draft of Letter to Applicant".

  
James L. McVey

12/18/98

initialed by M. Fanning *MF*. 12/21/98

cc:

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drafted by: J. McVey 40266na3.m

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*micro #3*

OFFICE OF GENERIC DRUGS

Microbiologists Review #4

February 2, 1999

- A. 1. ANDA: **40-266**  
APPLICANT: Bigmar Inc.  
9711 Sportsman Club Road  
Johnstown, Ohio 43031-1941
2. PRODUCT NAME: **Methotrexate for Injection, USP**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:  
Lyophilized Powder, 1 gram/bottle. Reconstitute with a sterile, preservative free, medium to a concentration of 50 mg/mL for IV, IA, IM and IT injection. Free Single Dose Vials.
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: anti neoplastic
- B. 1. DATE OF INITIAL SUBMISSION: July 31, 1997.  
2. DATE OF AMENDMENT:  
September 17, 1997.  
December 20, 1997.  
February 19, 1998.  
May 29, 1998.  
June 11, 1998.  
September 18, 1998.  
November 20, 1998.  
**January 19, 1999 - Subject of this Review.**  
**January 27, 1999 - Subject of this Review.**
3. RELATED DOCUMENTS: DMFs not reviewed. 40-263 preserved multi dose vials and 40-265 single dose vials.
4. ASSIGNED FOR REVIEW: February 2, 1999.
- C. REMARKS: Reviewed with sister products 40-265, non-preserved and 40-263 - preserved. The sterilization of equipment question is covered as with the other reviews.
- D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided in " " and "Microbiologist's.

initialialed by M. Fanning JS 2-2-99  
JS 2/2/99

cc: Original ANDA  
Duplicate ANDA  
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drafted by: J. McVey 40266a4.m



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*micro review # 4*