CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40266

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: **40-266**

Date of **Submissions: October 28, 1998**

Applicant's Name: **Bigmar, Inc.**

Established Name: **Methotrexate for Injection USP, 1 g/vial (Preservative Free)**

Labeling Deficiencies:

1. GENERAL COMMENTS:

   Please note that for computer-generated labeling to acceptable as final printed labeling, it must be true size, true color, and of good clarity. The package insert must be one contiguous piece.

2. CONTAINER

   a. Please note that the black writing on dark green is difficult to read due to insufficient background contrasting as described in 21 CFR 201.15(a)(6). Please revise.

   b. See GENERAL COMMENT.

3. CARTON

   a. Please note that the black writing on dark green is difficult to read due to insufficient background contrasting as described in 21 CFR 201.15(a)(6). Please revise.

   b. See GENERAL COMMENT.

4. INSERT

   Satisfactory in printers proof.

Please revise your container labels and carton and insert labeling, as instructed above, and submit 12 copies of final printed container labels along with 12 copies of final printed carton and insert labeling

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

_____

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? NO

Container Labels: (1 gram)

Carton Labeling: (1 gram)
Professional Package Insert Labeling:

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Methotrexate Sodium Injection

NDA Number: 11-719/S-095
NDA Drug Name: Methotrexate Sodium for Injection
NDA Firm: Lederle Laboratories

Date of Approval of NDA Insert and supplement #:
Approved May 20, 1997; Revised January 25, 1996).

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Labels in file folder and labels submitted in the side-by-side review.

Basis of Approval for the Carton Labeling: Labeling in file folder and labeling submitted in the side-by-side review.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an AND or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does AND meet them?		X	
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Methotrexate Sodium Injection; Lederle Laboratories; Approved May 20, 1997; Revised January 25, 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store between 15° to 25°C (59° to 77°F). Protect from light.

   ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Retain in carton until contents are used.

   USP: Preserve in containers for sterile solids as described under injection, protected from light.

   Chemist states the differences in the storage temperature are acceptable. See note from chemist on last labeling review.

4. Product Line:

   The innovator markets their product in preservative free and lyophilized powder. Each vial contains 20 mg, 50 mg, and 1 g.

   The applicant proposes to market their product in 1 g vials. Preservative free and lyophilized.

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 129, Vol. 1.1.

6. All manufacturing will be performed by Bigmar. All outside firms are utilized for testing. See pages 294 and 317, Vol. 1.1.

7. Container/Closure:

This product will be packaged in clear glass Type I with rubber stopper and orange plastic flip off cap and aluminum seals. See page 139, Vol. 1.1. and note from chemist on last labeling review.

Date of Review: **November 4, 1998**
Date of Submission: **October 28, 1998**

Reviewer: /S/ **Date:** 11/16/98

Team Leader: /S/ **Date:** 11/18/98

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cc:

ANDA 40-266
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Review

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

ANDA Number: **40-266**

Date of **Submissions: ~~October 28~~, 1998,** Nov. 25, 1998

Applicant's Name: **Bigmar, Inc.**

Established Name: **Methotrexate for Injection USP, 1 g/vial (Preservative Free)**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? YES

Container Labels: (1 gram) Satisfactory as of November 25, 1998 submission.

Carton Labeling: (1 gram) Satisfactory as of November 25, 1998 submission.
Professional Package Insert Labeling: Satisfactory as of November 25, 1998 submission.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Methotrexate Sodium Injection

NDA Number: 11-719/S-095
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Basis of Approval for the Container Labels: Labels in file folder and labels submitted in the side-by-side review.

Basis of Approval for the Carton Labeling: Labeling in file

folder and labeling submitted in the side-by-side review.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
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Packaging			
Is this a new packaging configuration, never been approved by an AND or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
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Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

,continued)	Yes	No	N.A.
...D make special differentiation for this label? (i.e., Pediatric strength vs ...c; Oral Solution vs Concentrate, Warning Statements that might be in red for ...e NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
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Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
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Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
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FOR THE RECORD:

1. Review based on the labeling of the listed drug (Methotrexate Sodium Injection; Lederle Laboratories; Approved May 20, 1997; Revised January 25, 1996).

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   Chemist states the differences in the storage temperature are acceptable. See note from chemist on last labeling review.

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   The applicant proposes to market their product in 1 g vials. Preservative free and lyophilized.

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 129, Vol. 1.1.

6. All manufacturing will be performed by Bigmar. All outside firms are utilized for testing. See pages 294 and 317, Vol. 1.1.

7. Container/Closure:

This product will be packaged in clear glass with rubber stopper and orange plastic flip off cap and aluminum seals. See page 139, Vol. 1.1. and note from chemist on last labeling review.

Date of Review: **December 7, 1998**
Date of Submission: **November 25, 1998**

Reviewer: /S/ **Date:** 12/9/98

Team Leader: **Date:**

/S/ 12/9/98

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cc:

/S/ 12/9/98

ANDA 40-266
DUP/DIVISION FILE
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Review

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

ANDA Number: **40-266**

Date of Submissions: **July 31, 1997 and December 20, 1997**

Applicant's Name: **Bigmar, Inc.**

Established Name: **Methotrexate for Injection USP, 1 g/vial**

Labeling Deficiencies:

1. CONTAINER (1 g)

   a. Revise the established name to read as follows:

      METHOTREXATE FOR INJECTION USP

   b. Revise to read "single dose vial" rather than

   c. Insert "Usual Dosage" prior to the "Consult package insert..." statement.

   d. To be in accord with 21 CFR 201.100(b)(3), include the routes of administration on the main panel.

   e. Include the following text "Discard Unused Portion" in the storage recommendations.

   f. Include the directions for reconstitution of this drug product as seen on the innovator's label.

   g. Replace the "Caution: Federal Law..." statement with "Rx Only". See Section ~~412 of Title IV~~ of the FDA Modernization Act of 1997 126 126

2. CARTON (1 x 100 mg, 1 x 200 mg and 1 x 250 mg)

See comments under CONTAINER.

3. INSERT

a. TITLE

Revise the established name to read:

METHOTREXATE FOR INJECTION USP

In addition, revise throughout the remainder of the text.

b. BOXED WARNING

i. Revise paragraph six to read as follows:

...involved and be...

[NOTE: Delete should.]

ii. Insert the following text as paragraph seven:

METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

iii. Number 5 - ...cough may require...

iv. Delete numbers This information does not appear in the latest approved labeling of the listed drug.

c. DESCRIPTION

To be in accord with USP 23, revise the molecular weight to read "454.45" rather than

d. CLINICAL PHARMACOLOGY

i. Paragraph three, third sentence - ...evidence suggests that...

ii. Pharmacokinetics is a subsection under CLINICAL PHARMACOLOGY. Revise the section heading so it has the same prominence as other subsection headings throughout the

insert.

iii. Pharmacokinetics, Metabolism - Insert the following text as the last sentence:

Methotrexate is partially metabolized by intestinal flora after oral administration.

e. WARNINGS

Insert a space between "WARNINGS" and "PRECAUTIONS".

f. PRECAUTIONS

i. Information for the Patients - Insert the following text as the second paragraph:

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

ii. Delete from the subsection heading "Carcinogenesis, Mutagenesis, Impairment of Fertility".

iii. Organ System Toxicity, Infection or Immunologic States - Revise the second paragraph to read as follows:

Opportunistic infections, including *Pneumocystis carnii* infections, have been reported rarely in patients receiving low dose methotrexate. when a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carnii* pneumonia should be considered.

iv. Neurologic, paragraph three - Revise the first sentence to read:

After the intrathecal...

v. Delete the subsection This information is not included in the latest approved labeling of the listed drug.

g. ADVERSE REACTIONS

i. Delete the subsections
This information is not included in the latest approved labeling of the listed drug.

ii. Central Nervous System - Revise the last sentence to read as follows:

...mood alteration or unusual cranial sensations.

iii. Skin - Delete the comma that appears between "erythema" and "multiforme", capitalize the "s" in "Syndrome" and revise the sentence to read as follows:

...necrolysis and Stevens-Johnson Syndrome.

iv. Urogenital System - Delete

v. Other rarer reactions - Revise to read as follows:

...vasculitis, opportunistic infection, arthralgia/myalgia...death and reversible lymphomas. Anaphylactoid...

vi. Adverse Reactions in Psoriasis -..."burning of skin lesions".

[NOTE: Insert "skin"].

h. DOSAGE AND ADMINISTRATION

i. Neoplastic Diseases

A) Revise paragraph one to read as follows:

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate injection may...

B) Paragraph two, first sentence - Insert "orally or" prior to "intramuscularly".

ii. Leukemia, paragraph two - Insert "either by

mouth or" prior to "intramuscularly" in the sixth sentence.

iii. Lymphomas - Revise to read as follows:

...Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

iv. Mycosis Fungoides - Insert the following text as the second sentence:

Dosage is usually 2.5 to 10 mg daily by mouth for weeks or months.

v. Psoriasis: Recommended Starting Dose Schedule - Insert the following text as number 2:

2. Divided oral dose schedule: 2.5 mg at 12 hour intervals for three doses.

i. HOW SUPPLIED

i. Delete title.

ii. See comment g under CONTAINER.

j. LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE - Delete the title "GUIDELINES FOR LEUCOVORIN DOSAGE AND ADMINISTRATION".

Please revise your container labels, carton and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research