CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40265

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: **40-265** Date of Submissions: **September 16, 1998**

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

Established Name: **Methotrexate Injection USP, 25 mg/mL (Preservative Free)**

Labeling Deficiencies:

1. CONTAINER (50 mg, 100 mg, 200 mg and 250 mg)

   Satisfactory in draft.

2. CARTON (1 x 50 mg, 1 x 100 mg, 1 x 200 mg and 1 x 250 mg)

   Satisfactory in draft.

3. INSERT

   a. TITLE

      We encourage the inclusion of "℞ only" in this section.

   b. BOXED WARNINGS

      Include the following to appear as boxed warnings 8, 9, 10.

      8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

      9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reaction have occurred within days of oral, intramuscular, intravenous, or intrthecal

methotrexate administration. Recovery has been reported with discontinuation of therapy.(See **PRECAUTIONS, Organ System Toxicity,** *Skin.*)

10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

c. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, and Impairment of Fertility.

Delete from this subsection title.

ii. Organ System Toxicity-Infection or Immunologic States

Revise the first sentence of paragraph two of this subsection to read as follows:

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

iii. Organ System Toxicity-Neurologic

Include the following to appear as sentences two and three of paragraph one of this subsection:

...irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic...

iv. Organ System Toxicity-Skin

Include the following to appear immediately following the Organ System Toxicity-Renal Subsection:

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

d. ADVERSE REACTIONS

i. Include the following to appear immediately after the Alimentary System subsection:

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

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

Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

iii. Include the following to appear immediately after the Central Nervous System subsection:

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections included nocardiosis; histoplasmosis, cryptococcosis, Herpes zoster, H. simplex hepatitis, and disseminated H. simplex.

iv. Skin-Revise this subsection to read as follows:

...necrolysis, Stevens-Johnson syndrome, skin necrosis, and exfoliative dermatitis.

v. Urogenital System

A. Revise the first paragraph of this subsection to read as follows:

...dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects.

B. Delete from the second paragraph of this subsection.

vi. Adverse Reactions in Psoriasis

Delete the last sentence of this subsection

With the exception...

e. HOW SUPPLIED

Revise your storage statement to include "Protect from light."

Please revise your container labels, carton and insert labeling, as instructed above, and submit 12 copies of final printed container labels for each strength, along with 12 copies of final printed carton labeling for each strength and 12 copies of final printed 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? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Professional Package Insert Labeling:

Revisions needed post-approval:

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

NDA Drug Name: Methotrexate Sodium Injection

NDA Firm: Lederle Laboratories

Date of Approval of NDA Insert and supplement #: May 20, 1997/S-095, 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/S-095; 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 at controlled room temperature 15° to 30°C (59° to 86°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 single-dose or in multiple dose containers preferably of glass, protected from light.

4. Product Line:

   The innovator markets their product in preservative free vials containing 50 mg, 100 mg, 200 mg and 250 mg.

   The applicant proposes to market their product in 50 mg, 100 mg, 200 mg and 250 mg preservative free vials.

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 158, Vol. 1.1.

6. All manufacturing will be performed by Bigmar. All outside firms are utilized for testing. See pages 335 and 358, Vol. 1.1.

7. Container/Closure:

   This product will be packaged in clear glass with grey rubber stoppers and aluminum seals with an orange flip off cap. See pages 1341, 1348 and 1353, Vol. 1.4.

8. This description of the finished dosage form "is a

clear solution". Page 1500, Vol. 1.4.

9. The innovator has a shared insert for three dosage forms - Tablets, Injection and For Injection. Several sections of the package insert were revised to exclude information pertaining to Rheumatoid Arthritis and the PO dosage form. The PO form, according to the D&A section is only indicated in the treatment of rheumatoid arthritis. The guidance document from 1988 also had this information deleted.

Date of Review: October 28, 1998

Date of Submissions: September 16, 1998

Reviewer: /S/ **Date:** 11/3/98

Team Leader: /S/ **Date:** 11/4/98

---

cc:

ANDA 40-265
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
X:\NEW\FIRMSAM\BIGMAR\LTRS&REV\40265NA4.L
Review

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

ANDA Number: **40-265** Date of Submissions: **November 25, 1998**
Amendment Date: **January 8, 1999**

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

Established Name: **Methotrexate Injection USP, 25 mg/mL (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: Satisfactory as of January 8, 1999 submission.

Carton Labeling: Satisfactory as of January 8, 1999 submission.

Professional Package Insert Labeling: Satisfactory as of ~~January 8, 1999~~ 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
NDA Drug Name: Methotrexate Sodium Injection
NDA Firm: Lederle Laboratories

Date of Approval of NDA Insert and supplement #: May 20, 1997/S-095, 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/S-095; 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 at controlled room temperature 15° to 30°C (59° to 86°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 single-dose or in multiple dose containers preferably of glass, protected from light.

4. Product Line:

   The innovator markets their product in preservative free vials containing 50 mg, 100 mg, 200 mg and 250 mg.

   The applicant proposes to market their product in 50 mg, 100 mg, 200 mg and 250 mg preservative free vials.

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 158, Vol. 1.1.

6. All manufacturing will be performed by Bigmar. All outside firms are utilized for testing. See pages 335 and 358, Vol. 1.1.

7. Container/Closure:

   This product will be packaged in clear glass with grey rubber stoppers and aluminum seals with an orange flip off cap. See pages 1341, 1348 and 1353, Vol. 1.4.

8. This description of the finished dosage form "is a clear solution". Page 1500, Vol. 1.4.

9. The innovator has a shared insert for three dosage forms - Tablets, Injection and For Injection. Several sections of the package insert were revised to exclude information pertaining to Rheumatoid Arthritis and the PO dosage form. The PO form, according to the D&A section is only indicated in the treatment of rheumatoid arthritis. The guidance document from 1988 also had this information deleted.

Date of Review: January 13, 1999
Date of Submission: November 25, 1998
Amendment Date: January 8, 1999

Reviewer: /S/ Date: 1/13/99

Team Leader: /S/ Date: 1/13/99

cc: /S/ 1/13/99

ANDA 40-265
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
X:\NEW\FIRMSAM\BIGMAR\LTRS&REV\40265.APL
Review