

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40266

BIOEQUIVALENCY REVIEW(S)

Methotrexate Sodium Injection, USP
1 g/vial (**Preservative Free**)
ANDA # **40-266**
Reviewer: Z.Z. Wahba
File #40266w.797

Bigmar, Inc.
Johnstown, OH
Submission Date:
July 31, 1997

REVIEW OF A WAIVER REQUEST

BACKGROUND

1. The firm has requested a waiver of in vivo bioequivalence study requirements for its drug product, Methotrexate Sodium Injection, USP, 1 g/vial. The reference listed drug (RLD) is Methotrexate Sodium Injection, USP, 1 g/vial (Lederle, NDA #11719).
2. The drug is indicated for the of neoplastic diseases (excluding meningeal leukemia, high dose methotrexate therapy, or intrathecal use) and severe psoriasis.

FORMULATION COMPARISON

Comparative compositions of the test and the reference products are as follows:

Comparison of Formulation

Ingredient	<u>Test Product</u> amount/vial	RLD amount/vial
Methotrexate Sodium (lyophilized powder)	1.0 g	1.0 g

- * Sodium hydroxide and/or hydrochloric Acid may be added (to the test or reference products) to adjust the pH to 8.5-8.7 during manufacturing.
- ** The methotrexate sodium 1 g/vial contains approximately 7 mEq of sodium.
- *** Methotrexate Sodium for injection should be reconstituted immediately prior to use with an appropriate sterile, preservative free medium such as 5% dextrose solution, USP, or sodium chloride injection, USP. The 1 g/vial should be reconstituted with 19.4 mL to a concentration of 50 mg/mL.

COMMENTS

1. The drug product is classified "AP" in the list of the

"Approved Drug Products with Therapeutic Equivalence Evaluations".

2. The test drug product is supplied as a lyophilized powder for injection use.
3. The test drug product contains the same active ingredients in the same strength and dosage form as the currently approved listed reference product
4. The waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Bigmar Inc. demonstrates that Methotrexate Sodium Injection, USP, 1 g/vial, falls under 21 CFR Section 320.22(b)(1) of Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for Methotrexate Sodium Injection, USP, 1 g/vial, of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Bigmar's Methotrexate Sodium Injection, USP, 1 g/vial to be bioequivalent to the reference listed product, Lederle's Methotrexate Sodium Injection, USP, 1 g/vial.

The firm should be informed of the recommendation.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-266

APPLICANT: Bigmar, Inc.

DRUG PRODUCT: Methotrexate Sodium Injection USP, 1 g/vial
(preservative free)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,


Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research