CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40265

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #40-265
SPONSOR: Bigmar, Inc.
DRUG: Methotrexate Sodium
DOSAGE FORM: Injection
STRENGTH: 25 mg/mL (Preservative Free)
REFERENCE PRODUCT: Lederle's Methotrexate Sodium Injection, USP, 25 mg/mL.
SUBMISSION TYPE: Waiver

STUDY SUMMARY: Not Applicable

DISSOLUTION: Not Applicable

WAIVER SUMMARY: The waiver of the *in vivo* bioequivalence study for the test product, Methotrexate Sodium Injection, USP, 25 mg/mL is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product formulation to be bioequivalent to the reference drug Lederle's Methotrexate Sodium Injection, USP, 25 mg/mL.

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III

INITIAL: /S/ DATE: 12/23/97

for GROUP LEADER: Ramakant Mhatre, Ph.D. BRANCH: III

/S/ 12/23/97

INITIAL: _____ DATE: _____

DIRECTOR: Dale Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: DPC DATE: 12/31/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: _____ DATE: _____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-265 APPLICANT: Bigmar, Inc.

DRUG PRODUCT: Methotrexate Sodium Injection USP, 25 mg/mL
(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,

1ST

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

Methotrexate Sodium Injection, USP
25 mg/mL (**Preservative Free**)
ANDA # **40-265**
Reviewer: Z.Z. Wahba
File #40265w.797

Bigmar, Inc.
Johnstown, OH
Submission Date:
July 30, 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, 25 mg/mL. The reference listed drug (RLD) is Methotrexate Sodium Injection, USP, 25 mg/mL (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	Test Product amount (mg/mL)	RLD amount (mg/mL)
Methotrexate Sodium	25 mg	25 mg
Sodium Chloride	0.490% W/V	0.490% W/V
Water for Injection	qs ad 100%	qs ad 100%
Sodium Hydroxide and/or Hydrochloric Acid	Adjust pH	Adjust pH (approximately 8.5)

* Methotrexate Sodium Injection (Preservative Free), Isotonic Liquid, for single use only, avaliable in 25 mg/mL, 4 mL (100 mg), 8 mL (200 mg), and 10 mL (250 mg) vials.

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 contains the same active and inactive ingredients in the same concentrations as the currently approved listed reference product

3. 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 (Preservative Free), USP, 25 mg/mL, 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, 25 mg/mL, of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Bigmar's Methotrexate Sodium Injection (Preservative Free), USP, 25 mg/mL to be bioequivalent to the reference listed product, Lederle's Methotrexate Sodium Injection (Preservative Free), USP, 25 mg/mL.

The firm should be informed of the recommendation.

CC: ANDA 40-265
ANDA DUPLICATE
DIVISION FILE
~~HFD-650/ Nerurkar for BioSign Off List~~ Done AN
HFD-658/ Z. Wahba Z Wahba
BIO DRUG FILE

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BIOEQUIVALENCY - ACCEPTABLE

1. **WAIVER** (WAI) Strengths: 25 mg/mL injection
Outcome: AC

OUTCOME DECISIONS:

AC - Acceptable

WINBIO COMMENTS:

/S/
Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ 12/12/97

Concur: /S/ Date: 12/31/97
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA #40-265, (original, duplicate), HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/102797/wp #40265w.797