CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40262

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #40-262
SPONSOR: Pharmachemie B.V.
DRUG: Leucovorin Calcium
DOSAGE FORM: Injection
STRENGTH: 350 mg/vial (lyophilized powder)
REFERENCE PRODUCT: Leucovorin Calcium for Injection, 350 mg/vial, manufactured by Immunex.
SUBMISSION TYPE: Waiver

STUDY SUMMARY: Not Applicable

DISSOLUTION: Not Applicable

WAIVER SUMMARY: The waiver of the *in vivo* bioequivalence study for the test product, Leucovorin Calcium for Injection, 350 mg/vial (lyophilized powder) is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product formulation to be bioequivalent to the reference drug Leucovorin Calcium for Injection (lyophilized powder), 350 mg/vial, manufactured by Immunex.

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

INITIAL: /S/ DATE: 12/23/

for GROUP LEADER: Ramakant Phatre, Ph.D. /S/ 12/23/97 BRANCH: III

INITIAL: _____ DATE: _____

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

INITIAL: /S/ DATE: 12/31/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: _____ DATE: _____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-262 APPLICANT: Pharmachemie B.V.

350 mg/vial
1/22/98

DRUG PRODUCT: Leucovorin Calcium for Injection 200 mg/vial

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,

/S/

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

Leucovorin Calcium Injection
350 mg/Vial
ANDA #**40-262**
Reviewer: Z.Z. Wahba
File #40262w.797

Pharmachemie B.V.
Haarlem, The Netherlands
Submission date
July 28, 1997

REVIEW OF A WAIVER REQUEST

BACKGROUND

1. The firm has requested a waiver of in vivo bioequivalence study requirements for its drug product, Leucovorin Calcium for Injection, 350 mg/vial (lyophilized powder). The reference listed drug (RLD) is Leucovorin Calcium for Injection (lyophilized powder), 350 mg/vial, manufactured by Immunex.

2. Leucovorin Calcium is indicated in the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible. The drug is also indicated for use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.

FORMULATION COMPARISON

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

Comparison of Formulation

Ingredient	Test Product amount/vial	RLD amount/vial
Leucovorin Calcium (lyophilized powder)	350 mg	350 mg
Sodium Chloride	140 mg	140 mg

* Sodium hydroxide and/or hydrochloric acid may be added (to the test or reference products) to adjust the pH to approximately 8.1 during manufacture.

** Leucovorin Calcium for Injection is indicated for intravenous or intramuscular administration and is supplied as a sterile lyophilized powder.

*** When reconstituted with 17 mL of sterile diluent

(bacteriostatic water which contains benzyl alcohol or sterile water), the solution will contain leucovorin calcium equivalent to 20 mg leucovorin per 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 and inactive 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 Pharmachemie B.V., demonstrates that Leucovorin Calcium for Injection, 350 mg/Vial, falls under Section 320.22 (b)(1) of Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation, Leucovorin Calcium for Injection, 350 mg/Vial, manufactured by Pharmachemie B.V. to be bioequivalent to the reference listed drug, Leucovorin Calcium for Injection 350 mg/Vial manufactured by Immunex.

The firm should be informed of the recommendation.

/S/

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

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ 12/15/97

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