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APPLICATION NUMBER

8-107/S-054

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 08-107/SLR-054		**Submission Date:**	February 22, 2001
Drug Name:	Leucovorin Calcium for Injection		
Formulation:	Injection		
Applicant:	Immunex Corporation 51 University Street Seattle, WA 98101		
Reviewer:	John Duan, Ph.D.		
Type of Submission:	Supplemental New Drug Application		

This is a review of the Clinical Pharmacology and Biopharmaceutics (CPB) studies submitted in support of a labeling change.

I. SYNOPSIS

Leucovorin is an active, chemically reduced derivative of folic acid, also known as folinic acid. The initial NDA (08-107) for leucovorin calcium was approved on June 20, 1952. The current submission provides a NCI monograph to support the change in the Clinical Pharmacology Section of the labeling. The following paragraph is to be added to the CLINICAL PHARMACOLOGY Section.

"The pharmacokinetics of 200 mg doses of Leucovorin administered intravenously and orally (reconstituted powder, not tablets) have been evaluated. The serum clearance corrected for bioavailability, terminal half-life, and apparent volume of distribution of total folate were not significantly different between the routes of administration. The oral bioavailability of the 200 mg dose was 31%. Eighty-three percent of the biologically active IV dose was recovered in the urine within 24 hours, 31% as 5-methyltetrahydrofolate. Twenty percent of the same oral dose was excreted in 24 hours, 16% as 5-methyltetrahydrofolate."

As supporting material, the monograph entitled "Absorption kinetics of orally administered leucovorin calcium" by B.W. McGuire et al. describes a dose proportionality and pharmacokinetics study of leucovorin. This study involved 30 healthy male subjects with mean age of 26 years (range: 19 to 45). Twenty-four subjects received 4 of 5 test doses (20, 40, 60, 80, and 100 mg) in a crossover fashion at 1-week intervals. Six separate subjects received 200 mg IV and oral in a 2-way crossover design. Blood and urine samples were collected.

The results showed that relative bioavailabilities were 78%, 62%, 49%, and 42% for the 40-60-, 80-, and 100-mg doses, respectively. Both the AUC and peak concentration (C_{peak}) of total folates (consisting predominantly of the major metabolite, 5-methyltetrahydrofolate), displayed significant deviation from linearity. This is consistent with a saturation of folate absorption previously reported.

Absolute bioavailability of the 200-mg oral dose of leucovorin based on AUC was 31% compared with that of the IV dose (6,848 vs. 22,298 ng•hr/ml). Total clearance, terminal halt-life, and apparent volume of distribution of total folate at the 200-mg dose were not significantly different between the two routes of administration. Eighty-three percent of the biologically active IV dose was recovered in the urine within 24 hours, 31% as 5-methyltetrahydrofolate. Twenty percent of the same oral dose was excreted in 24 hours, 16% as 5-methyltetrahydrofolate.

II. COMMENTS

1. The monograph provided supports the statements added in CLINICAL PHARMACOLOGY Section.

2. The added paragraph in CLINICAL PHARMACOLOGY Section:

The pharmacokinetics of 200 mg doses of Leucovorin administered intravenously and orally (reconstituted powder, not tablets) have been evaluated. The serum clearance corrected for bioavailability, terminal half-life, and apparent volume of distribution of total folate were not significantly different between the routes of administration. The oral bioavailability of the 200 mg dose was 31%. Eighty-three percent of the biologically active IV dose was recovered in the urine within 24 hours, 31% as 5-methyltetrahydrofolate. Twenty percent of the same oral dose was excreted in 24 hours, 16% as 5-methyltetrahydrofolate.

should be changed to:

The pharmacokinetics of 200 mg doses of Leucovorin administered intravenously and orally (reconstituted powder, not tablets) have been evaluated in healthy male subjects. The serum clearance corrected for bioavailability, terminal half-life, and apparent volume of distribution of total folate were not significantly different between the routes of administration. The oral bioavailability of the 200 mg dose was 31%. Eighty-three percent of the biologically active IV dose was recovered in the urine within 24 hours, 31% as 5-methyltetrahydrofolate. Twenty percent of the same oral dose was excreted in 24 hours, 16% as 5-methyltetrahydrofolate.

III. COMMENTS TO PROJECT MANAGER

1. This labeling is for LEUCOVORIN CALCIUM FOR INJECTION. However, the DOSAGE AND ADMINISTRATION Section indicates certain oral uses. The oral usage should be clarified .

IV. RECOMMENDATIONS

Please forward the Comments to the applicant.

/s/

John Duan, Ph.D. Date

Reviewer
Division of Pharmaceutical Evaluation I

/s/

Atiqur Rahman, Ph.D Date

Team Leader
Division of Pharmaceutical Evaluation I

CC:

NDA 08-107	original
HFD-150	Division File
HFD-150	PGarvey
HFD-150	BWhite
HFD-150	JJohnson
HFD-860	MMehta, ARahman, JDuan
HFD-48	Vishwanathan
CDR	

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Appendix I. Draft Labeling

Appendix II. Study synopsis

Study title: Absorption Kinetics of Orally Administered Leucovorin Calcium

Investigator: Brian W. McGuire, Luisa L. Sia, John D. Haynes, James C. Klsicki, Manuel L. Gutlerrez, and E. L. Robert Stokstad

Study period: not provided, NC1 Monograph 5:47-56, 1987.

Objectives: To study the oral dose proportionality and pharmacokinetics of leucovorin.

Subjects: Thirty healthy male subjects.

Study Design:

In a randomized crossover design, 24 fasted subjects were given 4 of a series of 5 single test doses between 20 and 100 mg, at 1-week intervals, of an oral solution of leucovorin calcium. Six separate subjects received 200 mg IV and po in a 2-way crossover. Blood and urine samples were collected over 24 hours for differential microbiological folate assays. Using L *casei* activity to measure total serum folates, the area under the concentration-time curve from 0 to infinite time (AUC_{inf}) was calculated.

Results:

Assay performance: Folates in the biological samples were measured by means of differential microbiological assays utilizing the growth response of the 2 folate-dependent organisms L. casei and S. faecalis. The assay validation results based on the monograph are presented in the following table.

Method	L. casei	S. faecalis
Sensitivity	0.5 ng folate/mL serum ($1.0X10^{-9}M$)	0.5 ng folate/mL serum ($1.0X10^{-9}M$)
Reproducibility (%CV)	4.8	6.9

Pharmacokinetics:

The results showed that relative bioavailabilities were 78%, 62%, 49%, and 42% for the 40-60-, 80-, and 100-mg doses, respectively. Both the AUC and peak concentration (C_{peak}) of total folates (consisting predominantly of the major metabolite, 5-methyltetrahydrofolate), displayed significant deviation from linearity. This is consistent with a saturation of folate absorption previously reported.

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In contrast to the nondose-proportionality observed in total serum folates, AUC of the small component *of S. faecalis* activity, which appeared earlier than 5-methyltetrahydrofolate, displayed linear kinetics, suggestive of a distinct mechanism of uptake. As dose increased,

S. faecalis activity increased in relative proportion to L. casei, indicating that saturation of the enzymatic bioconversion to 5-methyltetrahydrofolate may also be occurring.

Comments:

1. This study supports the statements added in the CLINICAL PHARMACOLOGY Section.

/s/

John Duan
3/29/01 12:53:45 PM
BIOPHARMACEUTICS

Atiqur Rahman
3/29/01 02:33:22 PM
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