CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

8-107/S-054

Administrative Documents

PROJECT MANAGER REVIEW OF LABELING

NDA: 8-107/SLR-054

Drug: Leucovorin Calcium for Injection

Applicant: Xanodyne Pharmacal, Inc.

Submission Dates:	October 27, 2000 February 22, 2001	**Receipt Dates:**	October 30, 2000 February 23, 2001

BACKGROUND:

DODP approved SLR-051 on July 21, 1997, which provided an additional statement to the WARNING section with reference #5 in the REFERENCES section.

DODP has not approved SLR-054 which is a Changes Being Effected supplement providing for labeling changes to the Geriatric Use subsection as directed in the CRF 201.57 (f) (10) (ii) (C) and (iii) (B).

DOCUMENTS REVIEWED:

I compared the FPL in SLR-054 to the labeling referenced in the SLR-050 approval letter dated May 24, 1996 and SLR-051 approval letter dated July 21, 1997.

The submission dated February 22, 2001 is the NCI monograph to supporting the additional paragraph added to CLINICAL PHARMACOLOGY section. This was reviewed by the clinical biopharmaceutics reviewer.

REVIEW:

I. Per our SLR-050 May 24, 1996 approval letter request, the following changes were made:

1. The last sentence in the DESCRIPTION section was revised to read:

   "One milligram of leucovorin calcium contains 0.002 mmol of leucovorin and 0.002 mmol of calcium."

2. The word "intravenous" was added to the first sentence in the WARNINGS section as follows:

   "In the treatment of accidental overdosages of folic acid antagonists, **intravenous** leucovorin should be administered as promptly as possible."

3. The last sentence of the first paragraph in the WARNINGS section was revised to read:

   "In the treatment of accidental overdosages of intrathecally administered folic acid antagonists, do not administer leucovorin intrathecally. LEUCOVORIN MAY BE HARMFUL OR FATAL IF GIVEN INTRTHECALLY.

4. In the DOSAGE AND ADMINISTRATION Advanced Colorectal Cancer section, the first paragraph was removed:

   "Leucovorin should not be mixed in the same infusion as 5-fluorouracil because a precipitate may form."

5. The following sentence was added after the two dosing regimens in the DOSAGE AND ADMINISTRATION Advanced Colorectal Cancer section:

   "5-Fluorouracil and leucovorin should be administered separately to avoid the formation of a precipitate."

6. The following sentence was moved from the beginning to the end of the DOSAGE AND ADMINISTRATION section and slightly revised to:

   "Leucovorin should not be mixed in the same infusion as 5-fluorouracil, since this may lead to the formation of a precipitate."

7. In the HOW SUPPLIED section "Leucovorin Calcium for Injection" was revised to read:

   "Leucovorin Calcium for Injection is supplied in sterile, single-use vials."

These changes are acceptable.

II. Per our January 3, 1997 letter, the following change was made:

The following paragraph was added to the end of the WARNINGS section:

"The concomitant use of leucovorin with trimethoprim-sulfamethoxazole for the acute treatment of Pneumocystis carinii pneumonia in patients with HIV infection was associated with increased rates of treatment failure and morbidity in a placebo-controlled study."

This change is acceptable.

III. Per our SLR-051 July 21, 1997 approval letter request, the following change was made:

1. The word "children" was changed to "pediatric" in the first sentence of the first paragraph in the Drug Interactions section. The language was changed in accordance to the Agency guidelines.

2. The storage statement in the HOW SUPPLIED section revised to read:

   "Store at 25°C (77°F); excursions permitted to 15 – 30°C (59-86°F)."

These changes are acceptable.

IV. The following additions were made under Changes Being Effected:

1. The following paragraph was added to the end of 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.[1]

   This change was reviewed by Dr. John Duan, clinical biopharmaceutics reviewer, on March 29, 2001 and found that the monograph provided supports for the statement. However, the addition of the statement "in healthy male subjects" should be added at the end of the first sentence as followed:

   The pharmacokinetics of 200 mg ... have been evaluated in healthy male subjects.

2. The following subsection was added to the end of the PRECAUTIONS section:

   Geriatric Use

   Clinical studies of Leucovorin Calcium did not show differences in safety or effectiveness between subjects over 65 and younger subjects. Other clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out. This drug is known to be excreted by the kidney and the risk of toxic reactions to the drug may be greater in patients with impaired renal function. Because elder patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

   The standard geriatric wording for drugs excreted by the kidney was reviewed by Dr. Robert White, medical officer, on August 20, 2001 and found to be acceptable.

3. Based on the clinical biopharmaceutics review dated March 29, 2001, the sponsor is requested to clarify oral usage. This labeling is for Leucovorin calcium for injection. However, the DOSAGE AND ADMINISTRATION Section indicates certain oral uses.

   Dr. Robert White, medical officer reviewed this, on January 23, 2002 and he found that the request for clarification from the sponsor was not necessary.

4. The previous references were removed and a reference for the new package paragraph was added.

   It is the policy of this division to include only safe handling references and only in the cytotoxic drugs labeling, and the applicant should be requested to delete the reference at the next printing.

V. Based on the Dr. White review dated January 23, 2002 the following recommendation should be done with the next printing.

   Under the **DOSAGE AND ADMINISTRATION** section, the last paragraph of the Advanced Colorectal Cancer subsection the following paragraph is outdated and should be deleted:

   "Several other doses and schedules of leucovorin/5-fluorouracil therapy have also been evaluated in patients with advanced colorectal cancer; some of these alternative regimens may also have efficacy in the treatment of this disease. However, further clinical research will be required to confirm the safety and effectiveness of these alternative leucovorin/5-fluorouracil treatment regimens."

CONCLUSION - RECOMMENDED REGULATORY ACTION:

Supplement SLR-054 should be approved with the requested that the applicant deletes the last paragraph in the Advance Colorectal Cancer subsection under the DOSAGE AND ADMINISTRATION section and the proposed reference be removed.

Patty Garvey, R.Ph.
Regulatory Project Manager

Concurrence:

Dotti Pease
Chief, Project Management Staff

This review was reviewed and signed off by:

Dotti Pease/ 2-9-01, 8-3-01, 1-10-02
Robert White, M.D./ 8-20-01, 1-23-02
Atik Rahman, Ph.D./ 2-14-01

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
2/5/02 11:34:46 AM
CSO

Dotti Pease
2/5/02 12:25:54 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 08-107/S-054

CBE-0 SUPPLEMENT

Immunex Corporation
Attention: Mark W. Gauthier
Senior Regulatory Affairs Manager
51 University Street
Seattle, WA 98101

Dear Mr. Gauthier:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Leucovorin Calcium for Injection

NDA Number: 08-107

Supplement Number: S-054

Date of Supplement: October 27, 2000

Date of Receipt: October 30, 2000

This supplemental application, submitted as a "Supplement - Changes Being Effected" supplement, proposes the following change(s): Geriatric Labeling Supplement.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 29, 2000 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

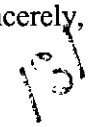
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Patty Garvey, Project Manager, at 301-594-5766.

Sincerely,



Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Original NDA 8-107/S-054
HFD-150/Div Files
HFD-150/P.Garvey

Filename: C:\My Documents\Immunex\N08107\Letters\Ack_SLR054.14Dec00.doc

SUPPLEMENT ACKNOWLEDGMENT

/s/

Patricia Garvey
12/14/00 12:08:29 PM
Signed for Dotti Pease