CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40262

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **40-262** Date of Submission: **July 28, 1997**

Applicant's Name: **Pharmachemie B.V.**

Established Name: **Leucovorin Calcium for Injection, 350 mg vial**

Labeling Deficiencies:

1. CONTAINER (350 mg)

   Satisfactory in draft.

2. CARTON (1 x 350 mg)

   Satisfactory in draft.

3. INSERT

   a. HOW SUPPLIED

      Add the statement "Retain in carton until time of use" following "Protect from light".

Please revise your container labels and carton and insert labeling, as instructed above, and submit final printed container labels along with final printed carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **40-262** Date of Submission: **July 28, 1997**

Applicant's Name: **Pharmachemie B.V.**

Established Name: **Leucovorin Calcium for Injection, 350 mg/vial**

Labeling Deficiencies:

1. CONTAINER (350 mg)

   a. Center Panel

      i. Revise to read "sterile single use vial" rather than "350 mg/vial".

      ii. Relocate the expression of strength to appear directly following the established name and revise the expression of strength to read as follows:

         Equivalent to leucovorin 350 mg

         [Note: Delete "/vial"]

      iii. We encourage you to differentiate this strength from your other product strengths (50 mg and 100 mg) by the use of boxing, contrasting colors or some other means.

      iv. Revise to read:

         For IV/IM use.

   b. Left panel

      i. Revise the temperature storage recommendations to read "Store between 15° to 25°C...".

      ii. Add the statement "Retain in carton until time of use" following "Protect from light"

c. Right panel

Revise to read "Usual Dosage" rather than "Usual dosage". In addition add the following as the second sentence:

Do not use preservative containing solution for doses greater than 10 mg/m^2.(See WARNINGS)

2. CARTON (1 x 350 mg)

a. See comments a, c, d and e under CONTAINER.

b. Revise to read "1 sterile single use vial".

3. INSERT

a. GENERAL COMMENT

We note you have stated that the insert will not include "usage of leucovorin in combination with 5-fluorouracil for colon cancer" before December 12, 1998. However, the insert provided for review contains this information in it. Please revise and/or comment.

b. We have provided a "mock-up" copy of the insert with our review comments. In addition, please revise the following:

i. Insert the following text to appear as the last paragraph:

Seizures and/or syncope have been reported rarely in cancer patients receiving leucovorin, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases or other predisposing factors, however, a causal relationship has not been established.

ii. REFERENCES

It is the current policy for oncology drug labeling to include only references pertaining to safe handling of oncologic drugs. Delete reference number one and insert the following text in its place:

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. JAMA, 1985; 253(11):1590-1592.

3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.

5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA - A Cancer Journal for Clinicians, 1983; (Sept/Oct) 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp Pharm, 1990; 47:1033-1049.

7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic)

Please revise your container labels and carton and insert labeling, as instructed above, and submit draft labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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