CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40262

CHEMISTRY REVIEW(S)

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 40-262

FIRM: Pharmachemie BV
Attention: Deborah Jaskot (Agent)
1510 Delp Drive
Kulpsville, PA 19443

DOSAGE FORM: Lyophilized powder for Injection

STRENGTH: (350 mg (base)/vial)

DRUG: Leucovorin Calcium

CGMP STATEMENT/EIR UPDATED STATUS:
The latest EER was issued 12/14/98 for the listed firms. The EER was initially completed and considered generally acceptable on September 15, 1997. An EER FUR was found acceptable for all applicable firms on 7/8/99.

Manufacturing, processing, packaging, labeling, and testing of the referenced drug product will be performed at:

Pharmachemie BV
Swensweg 5
NL-2031 GA Haarlem
The Netherlands

The Leucovorin Calcium nds is manufactured by:

BIO STUDY: Satisfactory. Pharmachemie BV has requested a waiver from the performance of an in-vivo Bioequivalence study, and the Division of Bioequivalence has granted the firm's request.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Yes. The container is identical to that described in the C/C section.

Glass Vial: is a 30.5 cc, 25R, 20mm, USP clear borosilicate glass vial;
Rubber Stoppers: 20 mm, gray 1292 (1.75 mm septum thickness)or 1319 (3.30 mm septum thickness) bromo butyl rubber stopper (#PH4002/45). The stoppers are specially developed for freeze-drying operations.
Snap Cap/Overseal: 20 mm plastic snap-cap and aluminum overseal:

LABELING: Pharmachemie responded to the 8/28/98 labeling review of T. Watkins on 3/12/99 with the submission of FPL. The FPL was found satisfactory as per Theresa Watkins/John Grace on 5/5/99 and 5/6/99 respectively. Refer to the Labeling Approval Summary in the ANDA (Vol. 3.1).

STERILIZATION VALIDATION (IF APPLICABLE): The ANDA submission is recommended for approval on the basis of sterility assurance as per L.Ensor/M.Fanning on 12/1/99.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?): Pharmachemie has manufactured a batch of vials of 350 mg/vial. (Refer to chemistry review #1 for the general manufacturing procedure).

Pharmachemie has provided a blank batch record for the maximum production size batch they intend to manufacture under the ANDA; a vial batch. Pharmachemie has indicated that they will not reprocess batches of the finished dosage form. If reprocessing is desired, a supplement to the application will be submitted.

Pharmachemie manufactured one batch of Leucovorin Calcium for Injection, 350 mg/vial; Lot #WRD0105. The batch was vials. An executed Batch record (both original and an english translation of the originals were submitted.

The source of the nds used in the manufacture of the referenced drug product was The DMF has been found acceptable. An amendment to the DMF was submitted on December 9, 1997 and was reviewed by this reviewer on January 21, 1998. The amendment was found satisfactory. A May 4, 1998 DMF Amendment was submitted and was reviewed and found adequate on July 15, 1998. No new amendments have been received since that time (as of 12/14/98).

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?): The bioequivalence batch manufactured in support of this ANDA was as described above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS

BIO/STABILITY?: The production batch size for the drug product will be vials, which is within the scale-up factor.

Manufacturing process for intended production size batch is same as for the exhibit/stability batch.

cc: ANDA #40-262
HFD-600/Reading File
HFD-625/K.Furnkranz/
HFD-625/M.Smela/12-2-99
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Approve

/S/ 2/8/99

/S/ 12/8/99

Chemistry Closed

Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. REVIEW NUMBER: Chemistry Review No. 4

2. ANDA: 40-262

3. NAME AND ADDRESS OF APPLICANT:
Pharmachemie B.V.
Attention: Hellen de Kloet
U.S. Agent for Pharmachemie B.V.
323 Davis Street
Northborough, MA 01532

4. LEGAL BASIS FOR ANDA SUBMISSION: Refer to Chem Review #1

5. SUPPLEMENT(S): N/A 6. DRUG NAME: N/A

7. NONPROPRIETARY NAME:
Leucovorin Calcium

8. SUPPLEMENT(S) PROVIDE(S) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:

7/28/97	ANDA submission (received on 7/29/97)
8/13/98	ANDA Amendment (received 8/14/98)
3/12/99	ANDA Fax Amendment
10/11/99	ANDA Minor Amendment (micro deficiencies)

FDA:

8/27/97	Receipt of ANDA letter (date acceptable for filing: 7/29/97)
2/12/98	N/A MAJOR Fax Amendment
2/11/99	N/A FAX Amendment
7/21/99	N/A MINOR Amendment

10. PHARMACOLOGIC CATEGORY: To diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists; and rescue after high-dose methotrexate therapy in osteosarcoma.

11. HOW DISPENSED: Rx

12. RELATED INDs, NDAs and DMFs:
Listed Drug: Leucovorin Calcium for Injection
Holder of NDA: Immunex Corporation (NDA #08-107)
Pharmachemie has 2 approved ANDA's for Leucovorin

Calcium: 89-628 (50 mg/vial), 89-915 (100 mg/vial)

DMF listed in FDA 356h:

DMF
DMF
DMF

13. **DOSAGE FORM**: Lyophilized powder for injection

14. **POTENCY AFTER RECONSTITUTION**: 20 mg/mL (350 mg/vial)

15. **CHEMICAL STRUCTURE AND NAME**:
Refer to the Package Insert labeling (p.42 of the ANDA) The information is satisfactory as per the current USP.

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

- All chemistry questions have been satisfactorily answered. On March 26, 1999 a Chemistry Closed review was completed indicating that the application was satisfactory for Chemistry, Manufacturing and Controls.

- A N/A Minor letter was issued to Pharmachemie on 7/21/1999 as a result of a microbiological review. Pharmachemie responded to the 7/21/99 N/A MINOR Amendment on October 11, 1999. Review of the 10/11/99 ANDA MINOR Amendment by the microbiologist is necessary.

- An EER FUR is acceptable as of 7/8/99.

18. **CONCLUSIONS/RECOMMENDATIONS**:
Chemistry closed.

19. **REVIEWER**:
Kenneth J. Furnkranz

DATE COMPLETED/REVISED:
10/18/99
Revised 10/20/99

cc: ANDA 40-262
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Division File
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Chemistry - Review # 4