CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-140

CHEMISTRY REVIEW(S)

NDA 20-140

TRADE NAME (levoleucovorin) for injection

Spectrum Pharmaceuticals, Inc.

Mark Sassaman, Ph.D.
Sarah C. Pope, Ph.D
Review Chemists

Office of New Drug Quality Assessment
Division of Premarketing Assessment and Manufacturing Science (Branch V)
for
The Division of Drug Oncology Products (HFD-150)

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5 (New formulation- Stereoisomer of a racemate drug approved earlier)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

NDA 20-140 was filed under section 505(b)(2) of the Federal Food Drug and Cosmetic Act. Leucovorin calcium has been marketed in the United States since 1952 (Hospira, NDA 08-107) as the *d,l-* mixture of epimers. This application is the first U.S. filing for the biologically active single isomer, levoleucovorin calcium (*l*-leucovorin calcium).

10. PHARMACOL. CATEGORY: antidote to folic acid antagonists

11. DOSAGE FORM: Lyophilized Powder for Injection [after reconstitution (INJ PWD LYO F/SOL)]

12. STRENGTH/POTENCY: 50 mg/vial (10 mg/mL after reconstitution). *Note: dosage follows the convention used for leucovorin calcium and is in terms of levofolinic acid equivalence.*

13. ROUTE OF ADMINISTRATION: Intravenous administration (infusion)

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

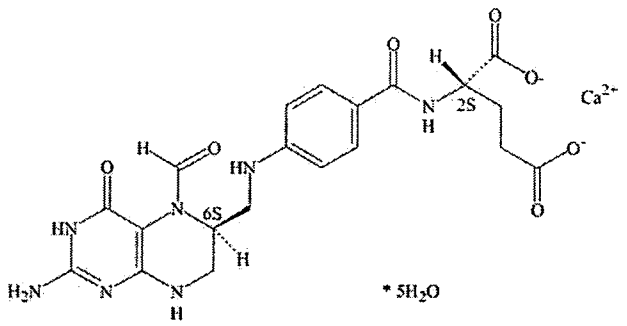
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s)	
(6S)-N-{4-[[(2-Amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl-L-glutamic acid, calcium salt (IUPAC name)	
N-[4-[[[(6S)-2-Amino-5-formyl-1,4,5,6,7,8-hexahydro4-oxo-6-pteridinyl]methyl]amino]benzoyl]-L-glutamic acid, calcium salt (1:1) (CA Index name)	
Empirical Formula	$C_{20}H_{21}CaN_7O_7.5H_2O$ (pentahydrate)
	$C_{20}H_{21}CaN_7O_7$ (anhydrous)
Molecular Weight	601.6 [calcium salt (pentahydrate)]
	511.5 [calcium salt (anhydrous)]
	473.4 (free acid form)
CAS Registry Number	[80433-71-2] (Calcium Levofolinate)
	[68538-85-2] (Folinic Acid [(6S)-isomer])

Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
20327	II	Merck Eprova AG	Calcium levofolinate pentahydrate	1	ADEQUATE	07 JAN 2008	Reviewed by Dr. M. Sassaman
[redacted]	III	[redacted]	[redacted]	3	ADEQUATE	07 OCT 2005	Reviewed by Dr. Jila Boal
[redacted]	III	[redacted]	[redacted]	3	ADEQUATE	01 NOV 2006	Reviewed by Dr. M Salazar
[redacted]	V	[redacted]	[redacted]	7	ADEQUATE	20 FEB 2008	See Microbiology Review by Robert J. Mello, Ph.D.

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NONE		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	14 FEB 2008	Entered by the Office of Compliance (CDER)
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	Consulted on the established name and strength harmony issue.		Rik Lostritto, Ph.D. Agreed with the proposed established name that does not include the name of the salt.
Methods Validation	Acceptable	20 FEB 2008	Methods are standard; no methods require post-approval validation.
DMETS	Consult-Review	13 DEC 2007	Richard Abate, Pharm.D. (currently awaiting confirmation of new trade name)
EA	Categorical Exclusion Claim under 21 CFR 25.31(a)- ACCEPTABLE	03 OCT 2007	Mark Sassaman, Ph.D.
Microbiology	ACCEPTABLE	20 FEB 2008	Robert Mello, Ph.D.

The Chemistry Review for NDA 20-140

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

All CMC deficiencies have been resolved satisfactorily. The reviewing microbiologist recommended approval of the NDA from the standpoint of product quality microbiology. The Office of Compliance issued an overall acceptable recommendation for the application. The applicant has accepted all revisions recommended in the labeling to date and has proposed two trade names. Both are pending review and acceptance from DMETS. All remaining comments pertaining to the labels and labeling, listed at the end of the review need to be communicated and resolved. From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is approvable, pending the submission of acceptable and final container/carton labels, including the Patient Information and Physician's Package Insert. An expiration dating period of 24 months is grantable. This information should be included in the letter along with the following statement on a CMC agreement.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

During the teleconference dated 25 FEB 2008, the Agency brought to your notice that — impurities listed in the drug product specifications have exceeded their identification thresholds and yet, their identities have not yet been established. Therefore, provide an agreement that the structural identity of the degradation products listed as — in the drug product specifications will be confirmed within six months from the date of approval of the NDA, and that the information will be submitted in the next annual report to the NDA. b(4)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, levoleucovorin calcium pentahydrate, is manufactured by Merck Eprova AG, Schaffhausen Switzerland, and described in their Type II DMF 20327.

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Merck Eprova AG been manufacturing the drug substance by the current method since 1997 and has produced over [redacted] batches since that time. Specifications for commercial material are identical to those found in the European Pharmacopoeia monograph entitled "Calcium Levofolinate Pentahydrate." The European Directorate for the Quality of Medicines and HealthCare (EDQM) recently issued a renewed Certificate of Suitability for Merck Eprova's Calcium Levofolinate Pentahydrate assuring its compliance with that monograph. Active pharmaceutical ingredients, which carry a Certificate of Suitability, are recognized by all signatory states of the European Union, Canada, Australia, and several other countries as acceptable for use in medicinal products.

b(4)

The drug product, Levoleucovorin calcium for Injection, is a sterile lyophilized powder which is packaged into a 10 mL Type I glass vial. [redacted]

b(4)

[redacted] The final product has a label claim of 50 mg/vial.

The Applicant's original resubmission included six months of real time, intermediate, and accelerated stability data for the drug product. These data were subsequently updated in submissions dated 17 DEC 2007 and 27 FEB 2008. The 17 DEC 2007 and 27 FEB 2008 stability updates also included statistical analyses of the real time stability data.

The Applicant's requested expiration dating period of 24 months (room temperature) is sufficiently supported by the provided stability data. Therefore, an expiration dating period of 24 months, when stored at room temperature, is approved.

B. Description of How the Drug Product is Intended to be Used

TRADE NAME (levoleucovorin calcium) for Injection is formulated as a sterile, lyophilized powder for reconstitution with Sodium Chloride Injection, USP. Each TRADE NAME vial contains 50 mg of levoleucovorin calcium per vial (See Section 12 – Strength/Potency). The reconstituted solution has a concentration of 10 mg/mL.

C. Basis for Approvability or Not-Approval Recommendation

In order for this NDA to be recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint, the following two items need to be satisfactorily resolved:

a) A final trade name (or confirmation of no trade name) should be submitted, and acceptable container/carton labels should be provided.
b) Acceptable final labeling, including the Physicians' Package Insert, should be submitted.

III. Administrative

A. Reviewer's Signature

Mark Sassaman, Ph.D.	29 FEB 2008
Sarah C. Pope, Ph.D.	29 FEB 2008
Ravi Harapanhalli, Ph.D.	29 FEB 2008

B. Endorsement Block

Chemist: Mark Sassaman, Ph.D./Date: 29 FEB 2008
Pharmaceutical Assessment Lead/Chemist: Sarah C. Pope, Ph.D./Date: 29 FEB 2008
Branch Chief: Ravi Harapanhalli, Ph.D./Date: 29 FEB 2008
Project Manager: Paul Zimmerman/Date: 29 FEB 2008

C. CC Block

Paul Zimmerman

57 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

Division of Oncology and Pulmonary Drug Products

Review of Chemistry, Manufacturing, and Controls

DEC 23 1991

NDA #:20-140

DATE REVIEWED: 23 December 1991

REVIEW #: 1

RECOMMEND ACTION: Not Approvable

REVIEW TEAM MEMBERS: Guiragos Poochikian,Ph.D.
Jeffrey Blumenstein, Ph.D.
John C. Leak, Ph.D.
Alan C. Schroeder, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original*	12/14/90	12/18/90	8/8/91
Amendment	6/11/91 (micro)		
Amendment*	9/20/91	9/26/91	10/8/91
Amendment	11/21/91 (micro)	11/22/91	

*subject of this review.

NAME & ADDRESS OF APPLICANT:
Lederle Laboratories
N. Middletown Rd.
Pearl River, NY 10965

Attn: Steven I Engle
Assoc. Dir., Regulatory Liason

DRUG PRODUCT NAME

Proprietary:	Isovorin for Injection
Established:	Levoleucovorin Calcium (USAN, proposed) for Injection l-Calcium folinate (INN) l-leucovorin calcium for injection (proposed)
Code Name/#:	CL 307,782
Chem.Type/Ther.Class:	2C

PHARMACOL. CATEGORY/INDICATION: Antidote to folic acid antagonists, for use as rescue therapy after high dose methotrexate treatment of osteosarcoma. After treatment with 12 g/m^2 methotrexate over 4 hours by i.v. infusion, levoleucovorin rescue is begun 24 hours after the start of methotrexate infusion. Levoleucovorin dosage is approximately 5 mg/m^2 every 6 hours for 10 doses.

DOSAGE FORM: for injection (sterile cryodesiccated powder).

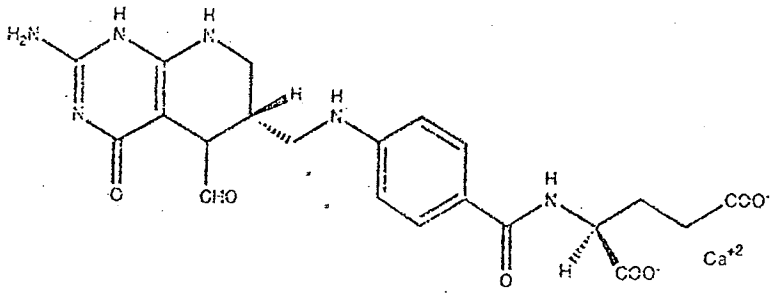
STRENGTHS: vials of —— 50 mg and —— *expressed as the free acid equivalent weight, i.e., of l-leucovorin). To be reconstituted with —— 5 mL and —— of sterile diluent, respectively, to yield 10 mg/mL in each case of levoleucovorin as the free acid. b(4)

ROUTE OF ADMINISTRATION: injection (for i.v. or i.m. use)

Rx/OTC: Px

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: $C_{20}H_{21}N_7O_7Ca$; MW 511.51 (473.45 free acid)

(6S)-N-[4-[[2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-Glutamic Acid calcium salt (1:1)



SUPPORTING DOCUMENTS:

Type	Number	Owner	Subject
Type 1 DMF	3124	Lederle Parenterals, Inc.,	Carolina, PR, facility No LOA (corporate relationship to applicant, confirmed by COMIS subject header for DMF
IND	[redacted]		[redacted] b(4)
NDA	8-107	Applicant	*dl*-leucovorin calcium injection & solution
NDA	18-459	Applicant	*dl*-leucovorin calcium tablet, 5 mg
ANDA	71-962	Applicant	*dl*-leucovorin calcium tablet, 10 mg
ANDA	71-104	Applicant	*dl*-leucovorin calcium tablet, 15 mg
ANDA	[redacted]		b(4)
DMF	[redacted]		
DMF	[redacted]		
NDA	20-141	Applicant	*l*-leucovorin calcium tablets (2.5mg, 5.0mg, 7.5mg, 12.5mg)

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
NDA	18-342	Burroughs Wellcome	Wellcovorin Tablets
ANDA	71-198	Barr	*dl*-leucovorin calcium tablet, 5 mg
ANDA	71-199	Barr	*dl*-leucovorin calcium tablet, 25 mg
ANDA	71-598	Par	*dl*-leucovorin calcium tablet, 25 mg
ANDA	71-600	Par	*dl*-leucovorin calcium tablet, 5 mg

CONSULTS:

1. Labeling and Nomenclature: A request for trademark review was submitted by Dr. Look to the Labeling and Nomenclature Committee on 3/8/91 for the proposed trademark (Isovorin®), and a memorandum was returned from Kent Johnson on 4/4/91 which did not find a problem with the proposed trademark.

2. Microbiology:
   A. Original Submission: A request for microbiological review was made by Dr. Sally Look on February 8, 1991, asking that a review be done on the sterility assurance and validation data in the NDA "from the perspective of manufacturing and controls, filling operations, closure integrity and final product release." Volumes 1, 4 and 5 of the NDA and DMF 3124 were sent with the request. Dr. Look indicated that she was later provided with general guidelines by the microbiologist for information required for aseptic fill manufacturing processes, and this information was sent by the CSO Mr. Zimmerman via facsimile transmission to the applicant.

   B. Amendment dated 6/11/91: The applicant responded with an amendment dated 6/11/91, this was reviewed by the microbiologist Dr. David Hussong on 8/13/91, and his draft deficiencies were sent by facsimile transmission to the applicant by Mr. Zimmerman on 8/27/91.

   C. Amendment dated 11/21/91: The applicant responded to the above concerns in an amendment dated 11/21/91, and the amendment has been forwarded on 11/25/91 by the CSO to the microbiologist for consult review. Currently Pending.

3. Environmental Assessment: The original submission was sent to HFD-102 on 2/8/91 concerning EA issues and was found to be severly deficient. An amendment to NDA 20-140 was received on 6/11/91 covering EA and Microbiology concerns. The EA portion was sent to HFD-102 on 7/2/91 for consultation. Currently Pending

REMARKS:

1. The applicant is being requested to contact the USAN Council concerning the established name for the active ingredient (see draft letter), since the existing USAN name, leucovorin calcium, is for a drug which is a diastereomeric mixture. (Note that the marketed drug is not a racemic mixture, since the amino acid portion is always L, it is a diastereomeric mixture. The proposed drug is a single diastereomer.)

2. Note that EERs have been requested by Dr. Sally Look on January 25, 1991 for facilities involved in the manufacturing of new drug substance and drug product, packaging and release & stability testing. A determination of CGMP status has not been received from HFD-320 so far, although the NDA is listed on Compliance's computer data base. An additional EER request was submitted on 11/21/91 to address the microbiologist's concerns for sterility at the Puerto Rico facility. (The microbiologist recommended in his conclusions to the 8/13/91 review that an inspection of the facility be done "to assess the appropriateness of transporting open vials from the fill rooms of both areas (Parenterals I and Parenterals II) to the lyophilizers in Parenterals I.")

3. Labeling cannot be fully evaluated at this stage, since it is in typed draft form and not presented in the format in which it will actually appear. Colors, sizes and positioning will need to be taken into consideration.

4. It is being requested that the applicant update the stability data, and provide data to demonstrate the microbiological quality of the reconstituted drug product on storage. When this data is provided, a consult review from the microbiologist should be requested.

5. Dr. Leak is requesting clarification on the number of suppliers of various sizes of glass vials for the drug product, as well as special treatment of the glass surface. The applicant's response should be considered relative to stability data which has been presented.

6. See microbiologist's review #1, dated August 13, 1991, for draft comments (deficiencies) concerning manufacturing and controls (amendment dated June 11, 1991) from the perspective of sterility assurance.

DRUG SUBSTANCE: Description, Manufacturer, Method of Manufacture, Process Controls and Specifications

ENVIRONMENTAL ANALYSIS

12/23/91
Jeffrey J. Blumenstein, Ph.D.
Review Chemist

DRUG SUBSTANCE: Analytical Methods and Container/Closure System
DRUG PRODUCT: Specification & Analytical Methods for Inactive Components, Analytical Methods and Container/Closure System and Methods Validation

John C Leak 12/23/91
John Leak, Ph.D.
Review Chemist

DRUG PRODUCT: Components & Composition, Manufacturer, Method of Manufacture and Packaging, Specifications, Stability, Microbiology and Labeling

Alan C. Schroeder 12/23/91
Alan C. Schroeder, Ph.D.
Review Chemist

CONCLUSIONS & RECOMMENDATIONS:

NDA 20-140 is not approvable from a chemistry perspective and the chemistry deficiency letter should be conveyed to the sponsor.

Guiragos Poochikian, Ph.D.
Chemistry Project Manager

cc:
Org. NDA 20-140
HFD-150/Division File
HFD-150/GPoochikian
HFD-151/PZimmerman
HFD-150/CHolberg
HFD-102/CKumkumian
HFD-150/JLeak
HFD-150/ASchroeder
HFD-150/JBlumenstein

28 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2