

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-140

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 20-140
BRAND NAME: ISO-Vorin™
GENERIC NAME: l-Leucovorin Calcium
DOSAGE FORM: 50 mg Vials for Intravenous Injection
INDICATIONS: Rescue Therapy after High Dose Methotrexate Therapy
SUBMISSION DATES: 29-Jun-2007 and 10-Aug-2007
SUBMISSION TYPE: NDA-Resubmission
APPLICANT: Spectrum Pharmaceuticals
DDOP: Division of Drug Oncology Products
OCP DIVISION: Division of Clinical Pharmacology 5
OCP REVIEWER: Sophia Abraham, Ph.D.
OCP TEAM LEADER: Brian Booth, Ph.D.

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1. EXECUTIVE SUMMARY

Spectrum Pharmaceuticals submits a New Drug Application (NDA 20-140) for ISO-Vorin™ (l-leucovorin calcium) for Injection to address the FDA Deficiencies cited in the letter of 03-Jan-1992 (see Appendix 2). Most of these deficiencies were related to some Chemistry, Manufacturing, and Controls (CMC) issues. The original NDA 20-140 was submitted for ISO-Vorin™ on 14-Dec-1990 to seek the indication for the use of ISO-Vorin™ as a rescue therapy after high-dose methotrexate therapy for osteosarcoma.

The current package insert for ISO-Vorin™ for Injection was revised with respect to CMC for both drug product and drug substance and to update the safety data. The Applicant submitted the revised package insert in the PLR (Physician Labeling Rule) format. We reviewed the CLINICAL PHARMACOLOGY/ Pharmacokinetics section of the PLR revised labeling for correctness of content compared to the original labeling. Labeling information regarding the _____ was deleted from the Pharmacokinetics subsection. No changes were made in the pharmacokinetics of leucovorin following the intravenous route. [The original clinical pharmacology review of 1990 for this NDA is shown in Appendix 3].

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1.1 RECOMMENDATION

NDA 20-140 submitted in support of ISO-Vorin™ (*l*-leucovorin calcium) for Injection is acceptable to the Office of Clinical Pharmacology. Please forward the Clinical Pharmacology Labeling Recommendations to the Applicant as outlined under section 3 of this review (pp. 5).

1.2 PHASE 4 COMMITMENTS

[None]

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Please see attached the original clinical pharmacology review for this NDA (Appendix 3)

2 QUESTION BASED REVIEW

2.1 *General Attributes of the Drug*

- 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?
- 2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?
- 2.1.3 What are the proposed dosage(s) and route(s) of administration?

2.2 *General clinical pharmacology*

- 2.2.1 What are the design features of the clinical studies used to support dosing or claims?
- 2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD) and how are they measured in clinical pharmacology and clinical studies?
- 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

2.2.4 Exposure-response

- 2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

- 2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?
- 2.2.4.3 Does this drug prolong the QT or QTc interval?
- 2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?
- 2.2.5 What are the PK characteristics of the drug and its major metabolite?
 - 2.2.5.1 What are the single dose and multiple dose PK parameters?
 - 2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
 - 2.2.5.3 What are the characteristics of drug absorption?
 - 2.2.5.4 What are the characteristics of drug distribution?
 - 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?
 - 2.2.5.6 What are the characteristics of drug metabolism?
 - 2.2.5.7 What are the characteristics of drug excretion?
 - 2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?
 - 2.2.5.9 How do the PK parameters change with time following chronic dosing?
 - 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

2.3 *Intrinsic Factors*

- 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?
- 2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?
 - 2.3.2.1 Elderly
 - 2.3.2.2 Pediatric patients
 - 2.3.2.3 Gender
 - 2.3.2.4 Race
 - 2.3.2.5 Renal impairment
 - 2.3.2.6 Hepatic impairment
 - 2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?
 - 2.3.2.7 What pregnancy and lactation use information is there in the application?

2.4 *Extrinsic Factors*

- 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions

- 2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?
- 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?
- 2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?
- 2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
- 2.4.2.5 Are there other metabolic/transporter pathways that may be important?
- 2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?
- 2.4.2.7 What other co-medications are likely to be administered to the target patient population?
- 2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?
- 2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?
- 2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

2.5 General Biopharmaceutics

[NOT APPLICABLE]

- 2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?
- 2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?
 - 2.5.2.1 What data support or do not support a waiver of in vivo BE data?
 - 2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?
 - 2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?
- 2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?
- 2.5.4 When would a fed BE study be appropriate and was one conducted?
- 2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?
- 2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?
- 2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

2.6.2 Which metabolites have been selected for analysis and why?

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

2.6.4.2 What are the lower and upper limits of quantification (LLOQ)?

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

3. OCPB Labeling Recommendations

12. Clinical Pharmacology

12.3 Pharmacokinetics

The pharmacokinetics of levoleucovorin after intravenous administration of a 15 mg dose was studied in healthy male volunteers. After rapid intravenous administration, serum total tetrahydrofolate (total-THF) concentrations reached a mean peak of 1722 ng/mL. Serum 1-5-methyl-THF concentrations reached a mean peak of 275 ng/mL and the mean time to peak was 0.9 hours. The mean terminal half-life for total-THF and 1-5-methyl-THF was 5.1 and 6.8 hours, respectively.

APPEARS THIS WAY ON ORIGINAL

8 Page(s) Withheld

 Trade Secret / Confidential (b4)

 x Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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Responses to the deficiencies for levoleucovorin calcium are provided below. Please note that the observations below (from 18 to 30) are related to drug product batches submitted by Lederle Laboratories in their original submission. This submission includes the information on product batches made at Chesapeake Biological Laboratories, Inc., on behalf of Spectrum Pharmaceuticals. All questions raised are addressed in the manufacture of these new batches. For reviewer's convenience, the information is provided in the response where the information is new. In many instances, hyperlinks are provided in the response where appropriate information can be obtained.

18) *The following comments are concerned with components, composition and batch formula of the drug product.*

18.a. *In drug product manufacture, the targets for filling vials should be the same as the claimed amounts on the label. The use of an overage of drug is not warranted and will lead to superpotent drug concentration when the vials are reconstituted according to the labeling.*

Spectrum Pharmaceuticals, Inc. manufactured new conformance lots of levoleucovorin calcium injection vials without added overages in the drug product.

_____ prior to lyophilization. The lyophilized product is reconstituted with 5.3 mL of sterile diluent resulting in a drug concentration of 10 mg/mL. _____ of drug solution is withdrawn from the vial to provide a dose of 50-mg levoleucovorin per vial.

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18.b. *The batch formulas provided (Vol. 4, pp. 4-6) should be modified in accordance with the changes in production scale proposed in your amendment dated 9/20/91.*

The question is not relevant at this point since new conformance lots of the drug product were manufactured at the new manufacturing site – Chesapeake Biological Laboratories, Inc. in Baltimore, Maryland. The batch formula statements have been updated accordingly.

18.c. *Composition and batch formulas should list the actual amounts of L-leucovorin calcium used, in addition to the free acid equivalents.*

The composition and batch formula for 50 mg/vial dosage strength are included in the stability batch records 2100-102, 2100-103 and 2100-104.

18.d. *The statements of drug product components and composition should be modified to indicate that the proposed drug product will be manufactured with compendial grade (NF) sodium hydroxide and hydrochloric acid (as indicated in your footnote on page 3, Volume 4).*

Material code numbers and specification grades on drug product component and composition statements show the use of compendial grade mannitol, sodium hydroxide and hydrochloric acid.

18.e.

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- 18.f. The specifications for microbial limits for mannitol should include numerical limits for total organisms and the absence of certain organisms.**

The Quality Control monograph for mannitol has been updated to include specifications for microbial limit of _____ see section 1.1 of Control of Excipients of this submission.

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- 19) Please provide to the NDA the street address of the manufacturing, packaging and testing facility, rather than a box number.**

The new conformance (stability) batches were made in a new manufacturing site. The address for this site is: Chesapeake Biological Laboratories, Inc., 1111 South Paca Street, Baltimore, MD 21230-2591. The Manufacturer section of the submission has the name and addresses of all manufacturing and testing sites.

- 20) The ensuing remarks are with regard to the method of manufacture of the drug product.**

- 20.a Additional information should be provided concerning lots of drug product used in the clinical studies, to allow evaluation of the batch sizes proposed. This information should include the manufacturing scale, the manufacturing process used, site of manufacture and stability data (if available) for each clinical lot.**

No drug product manufactured at CBL has been used in the clinical trials to date. Vials from Lot 2100-104 (the first Process Validation lot) may be used in the Phase IV clinical studies. This information will be submitted to the Agency when the clinical studies will be initiated.

- 20.b. All equipment used, equipment capacities and the nature of the surfaces which come in contact with drug product should be described for the manufacturing process, including the cryodesiccation and packaging operations.**

The Description of Manufacturing Process and Process Control section of the submission lists equipment used, their capacities and the nature of material surface contacting the product during its manufacture.

- 20.c. In the master formula, it should be clarified who is responsible for determining the actual amount of l-leucovorin calcium to be used, and how it is calculated.**

The formulation operator is responsible for determination of the actual amount of levoleucovorin calcium and verification of the calculations is performed by a supervisor or designee during batch manufacture. Signatures of the operator and supervisor are required in the formulation section of the Manufacturing Batch Record (MBR) record on the calculation sheet. The MBR shows the equation for calculation of the amount of levoleucovorin calcium (actual). Spectrum issued the Certificate of Analysis to CBL for each API lot used in manufacturing of the batches. The potency and moisture values for the API were used to calculate the amount of API to be weighed in each batch.

- 20.d. The following differences in master formula have been noted between the original NDA and 9/20/91 amendment for all vial sizes.**

20.d. (1) The top _____ steps on page 2 of the master formula of the 9/20/91 amendment indicate that temperature should not exceed _____ whereas in the original NDA it

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states that it should not exceed — This should be clarified. What does the operator do if the temperature does exceed — and what are the consequences for the drug product?

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20.d.(2). In the 9/20/91 amendment, step 4 (page 2) has been added to the procedures. The statement " — " should be clarified. When is it necessary?

This statement has been removed in the new Process Validation Batch Record. The temperature of the sample solution is allowed to c —
— No further temperature adjustment is performed on the bulk product.

20.e. There seems to be a discrepancy between the procedures on page 27, Vol. 4 and the clinical trial batch records (e.g., pg. 70, Vol. 4) concerning the —

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This should be clarified.

The lyophilization cycle has been modified to accommodate the equipment at Chesapeake Biological Laboratories. See Manufacturing Process and Control section of this submission.

20.f. The filling procedures to be used should also be summarized.

Section 1.2.3 of the Description of Manufacturing Process and Process Control of this submission summarizes the —

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21 The following information should be provided concerning in-process tests and limits for manufacture of the drug product.

21.a. In-process tests and specifications for ensuring that the product is — and lyophilization is complete should be provided.

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21.b. All in-process controls should be summarized in one place.

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Section 3.2.P.3.4 Control of Critical Steps of this submission summarizes all in-process controls employed during the manufacturing process.

- 21.c. *The weight specification for the fill dose during filling of the vials should be provided.*

Section 1.1.4 of Control of Critical Steps of this submission provides the fill weight specification of _____

b(4)

- 21.d. *According to the clinical trial batch records, during filling, the fill dose weight is checked every _____*

_____ *The justification for this difference should be provided.*

b(4)

The comments are not applicable to this filing. We are pursuing only one product strength – 50 mg per vial. In the Spectrum's batch record, weight checks are performed at _____ the total batch size intervals - see Section 1.1.4 of Control of Critical Steps of this submission

22. *In regard to release testing of the drug product, you should describe the sampling plan that will be used to assure that the samples of the drug product obtained for release and stability testing are representative of the batch. The plan should include both the sampling of production batches and the selection of sub-samples for analytical testing.*

The sampling plan for each sample that is tested is included with each batch record.

23. *The following comments are concerned with drug product regulatory specifications.*

- 23.a. *The assay specification should be tightened.*

New assay specifications are submitted based on the Lederle's stability data.

- 23.b. *There should be a quantitative specification for particulates in the constituted solution.*

Quantitative specifications for particulate matter of the reconstituted product are submitted in the Specifications section of this submission.

- 23.c. *The proposed specifications for all related compounds and for moisture should be tightened.*

New related compound and moisture specifications are submitted based on the Lederle's stability data.

- 23.d. *Supporting data (e.g., pharmacological or toxicological information) should be provided or referenced concerning the safety of related compounds which may be present in the drug, or else details should be provided concerning the levels at which individual related compounds were present in lots for pivotal clinical studies.*

All the impurity limits for the lyophilized product are within ICH guidelines.

- 23.e. *Specifications for "constituted solution", "uniformity" and "sterility" should be spelled out rather than to state that they meet the requirements of the test. The NDA monograph should make reference to USP for the content uniformity test rather referencing a letter (pg. 123, vol.4).*

The Specifications section of this submission is updated to spell out the proper specifications.

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- 23.f. *Identification specifications should also indicate approximate wavelength maxima and minima values for the UV procedure, and an approximate retention time for the HPLC method.*

The Specifications section of this submission is updated to include _____, as the second identification test.

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- 23.g. *There should be a regulatory specification and method for the d-isomer in the drug product.*

A new _____ has been developed to quantify the d-isomer in the product. The levels of the d-isomer in the three API lots used in the conformance lots are listed in the Specifications section of this submission.

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- 23.h. *The specification range for pH appears too wide _____, since all data presented (volume 5, pages 137, 141, 145, 187, 193, 197, 238, 242 and 246) show a maximum variation between _____ A range of _____ seems reasonable.*

Although the in-process pH specification immediately after the adjustment and q.s. is set to _____ (CBL sample # QC1), the in-process pH specification for the first two batches were set at _____ (CBL sample # FF1) based on the data from the original NDA. However, after performing the product hold time study, the in-process pH specification was tightened to _____. The in-process pH testing result from the stability batches are provided in Section 2.1.1 of Control of Critical Steps and the pH results of the reconstituted final product are included in section 1.1 of Batch Analysis section of this submission. Upon further data from the validation batches, the pH range for the product may be updated.

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24. *The clarifications indicated below should be provided regarding your certificates of analysis for the drug product.*

- 24.a. *The samples or standards used for the chromatograms provided along with the certificates of analysis should be identified, in order that they may be evaluated.*

The chromatograms are provided along with the certificates of analysis in the section 3.0 of Batch Analyses section of this submission.

- 24.b. *Certificates of analysis should be modified to show individual impurities and degradation products for "other related compounds", to be consistent with the specification.*

Certificates of Analyses have been updated in section 2.0 of Batch Analyses to reflect the "Specified unidentified substance" and "Unspecified related substance".

25. *The following concern the container-closure system:*

- 25.a. *Clarify whether or not the rubber stoppers _____ If so, the composition of the _____ agent and procedures used should be provided.*

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- 25.b. *The bottles are to be obtained from a variety of vendors according to the specification sheets on pages 76 and 79 of volume 5, even though the lists on pages 73-75 indicate*

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only _____ as the supplier. The suppliers for the vials to be used to package the drug product should be clarified.

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In the new manufacturing facility at CBL, vials were obtained from only one source. _____

- 25.c. Test data on the vials should be supplied to show that the type I glass complies with the requirements of USP.

The data on the vials are supplied in section 6.0 of Container Closure System of this submission.

- 25.d. The specification sheets indicate that the _____ and the _____ Test data on the vials should be supplied.

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The new manufacturer (CBL) uses _____ with specifications and data described in section 5 of Container Closure System.

- 25.e. A letter of authorization to refer to DMF _____ support of the NDA should be provided.

Letters of authorization for the new manufacturers are supplied section 1.4.1 of this submission.

26. The comments listed below are with regard to your stability protocol for the drug product.

- 26.a. Your 9/20/91 amendment mentions addition of a test for particulate matter to the stability protocol. Is this a quantitative test? Test procedures and specifications should be provided for particulates.

We have manufactured new conformance lots and are conducting a new stability program. Reconstituted samples of the final product are tested for particulates by _____. Test results are included in section 5.0 of the Stability Data.

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- 26.b. Reconstituted samples should be examined for evidence of precipitation with time after initial dissolution. It should be indicated which specific solutions are to be used to reconstitute the drug product in stability testing.

A "reconstitution study" of l-leucovorin calcium for injection with 0.9% sodium chloride has been performed on 6-month stability samples stored at 25°C±2°C/60% ±5% RH. The study data with particulate analysis results are included in the Stability Data section of this submission.

- 26.c. An appropriate pyrogenicity test should be included in the stability protocol at appropriate intervals.

The new stability protocol calls for pyrogen testing by LAL in section 2.0, Appendix 3 of Stability Summary and Conclusion of this submission.

- 26.d. The sterility test should be performed at least annually on stability lots.

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The new stability protocol requires annual sterility testing of the stability samples in section 2.0, Appendix 3 of Stability Summary and Conclusion of this submission.

26.e. The sampling plan should be provided.

The new stability protocol outlines a sampling plan in section 2.0, Appendix 3 of Stability Summary and Conclusion of this submission.

26.f. The detailed protocol for statistical analysis of the stability data should be provided.

The detailed protocol for statistical analysis of the stability data will be submitted with the nine-month stability data.

26.g. At the present time, you should withdraw your proposal to extend the expiration dating period in accordance with 21 CFR 314.70(d)(5) for each container size based on full shelf-life data. The basis for this request is the use of a _____ in your current drug product batches on stability (vol. 4 page 9). This overfill would bias the stability results used to calculate the expiration dating period.

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No overage is used for stability samples.

26.h. Since product is to be labeled for storage at controlled room temperature _____ room temperature testing should be conducted at the upper limit of that range (i.e., _____)

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Per the ICH guidelines, the product needs to be stored at 25°C. We have samples at 30°C/65%RH in the new stability program up to 1 year – See section 1.2 of Stability Summary and Conclusion.

26.i. Please indicate whether all stability tests are performed at all test intervals (except sterility).

The stability tests and corresponding intervals are shown in the section 1.3 of Stability Summary and Conclusion.

26.j. Are stability specifications identical to product specifications (vol. 4, pg. 99-104)? This should be detailed in the stability protocol, including any differences.

The Specification section of this submission has two sets of specifications for release and stability testing.

26.k. The wording should be changed from “three initial production batches” (to be placed on stability) to “the first three production batches.”

Section 1.0 of Post Approval Stability Protocol and Stability Commitment mentions “first three production batches” must be placed on stability.

26.l. There is to be only one approved stability protocol, therefore the test intervals for “subsequent yearly monitoring batches” should be the same as for the initial three production batches. A modification of this protocol may be proposed after approval of the NDA through a supplemental NDA, based on accumulated stability data on production lots.

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We have included the new Stability Protocol in this submission. The test intervals for “subsequent yearly monitoring batches” will be the same as for the initial three conformance lots. Any modification of the protocol will be first proposed to FDA and an approval will be sought.

- 26.m. Concerning your stability commitment (pg. 30, September 20, 1991 amendment), you are reminded that any change in materials comprising the container-closure for the marketed drug product, in the bulk active ingredient supplier, in product formulation, or any significant change in manufacturing procedures will require prior approval of a supplemental NDA.**

All appropriate changes are included in this new submission (see above responses). We will seek a prior approval if we make any changes in the process or components of Specifications.

- 26.n. It should be clarified if stability testing of the reconstituted drug product as described in your amendment dated 9/20/91 will be routinely performed as part of the stability protocol for marketed drug product (e.g., first three production batches, etc.).**

The stability of l-leucovorin calcium for injection after reconstitution with 0.9% sodium chloride will be performed on 6-month stability samples stored at 25°C±2°C/60% ±5% RH. A sample protocol will be issued at that time.

- 26.o. Please clarify the methodology of the “safety test” in the ongoing stability protocol (e.g., pg. 153, vol. 5) and the meaning of the “test depts.” and method numbers. Detailed descriptions of methods should be provided (i.e., the notation USP XXI is not sufficient).**

Non-clinical pharmacological and toxicological studies have provided enough information on the safety of l-leucovorin for human usage (NDA 20-140, Volume 1, Section E). Current chromatographic analysis obviates the need for the “safety testing”. The safety test is therefore not included in the marketed product stability protocol or in the drug product monograph. Routine microbial and pyrogen testing will be conducted on all the drug product batches.

- 26.p. It should be clarified that “other related compounds” will be reported as individual compounds.**

Other related compounds will be reported as “specified unidentified substances” and “unspecified related substances” – see the Specifications section of this submission.

- 27. The ensuing remarks are in regard to your proposed stability report format.**

- 27.a. We recommend that as part of the stability report, the batch number of the drug substance used to make each drug product in the stability study, as well as the manufacturers of the container-closure components be included.**

The batch number for the drug substance and the manufacturers for container-closure components are included in section 1.1 of Stability Data section of this submission.

- 27.b. The date of packaging of the drug product, batch size and test method numbers should also be provided.**

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The drug product will be packaged prior to commercial release. The manufacturing date and batch sizes are included in section 1.1 of Stability Data section of this submission. The methods are specified in the Specifications section.

- 27.c. *Along with the names of the drug product and drug substance manufacturers, the sites of the facilities where drug product and drug substance were manufactured should be listed.*

The drug substance was manufactured by _____
The details on the facility where the API was manufactured were listed in the DMF. The drug product was manufactured by Chesapeake Biological Laboratories located at 1111 South Paca Street, Baltimore Maryland.

28. *The following comments concern the stability data which you have provided.*

- 28.a. *The stability data provided do not support a 2-year expiration dating period, nor do they support a labeling statement which specifies storage at 1 _____. You should update the data and provide a statistical analysis in support of the expiration dating period, along with a description of the statistical methods used. In addition, stability specifications should be tightened to be more in accordance with the data from the clinical lots.*

We are requesting expiration dating based on the new Stability Data in the Stability Summary section of this submission.

- 28.b. *Stability data provided for "other related compounds" appear to be given as the sum of individual compounds, which are not specifically identified. These data are quite variable and they are difficult to interpret without knowing what is happening to individual impurities and degradation products. Results should be listed by individual impurity and degradation product, and unidentified compounds should at least be listed by relative retention times.*

New Stability Data is provided for the new batches with individual impurities in the Stability Data section of this submission.

- 28.c. *You should indicate the minimum quantifiable amount of d-leucovorin in the drug product, and if less than _____, the actual data for d-leucovorin should be provided so that any trends may be seen (e.g., is there any detectable increase in d-leucovorin over time in the drug product?).*

The LOQ for the d-leucovorin in the product is _____ So far, no trend has been observed in terms of % d-leucovorin and the stability condition.

- 28.d. *Reconstitution studies conducted at 23°C for up to 7 days (e.g., vol. 5, pg. 239) do not seem to address the possibility of racemization of l-leucovorin in solution. Data should be provided to assure its stability under such circumstances.*

A "reconstitution study" of l-leucovorin calcium for injection with 0.9% sodium chloride has been performed on 6-month stability samples stored at 25°C±2°C/60%±5% RH for 24 hours. All d-leucovorin data are well below the limit of no more than 0.3%.

- 28.e. *Some stressed stability data (e.g., 40°C/75% relative humidity) should be provided for these samples to assess resistance of container-closure to moisture.*

ISO-Vorin™ (levoleucovorin calcium) for Injection
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NDA 20-140

The stability protocol does include testing for moisture content for storage at 40°C/75%RH (see section 1.0 of Stability Data section of this submission)

- 28.f. Lots of the drug substance used to make the stability lots of the drug product should be identified.**

The batch number for the drug substance are included in section 1.1 of Stability Data section of this submission.

- 28.g. The sampling plan used for the stability studies underway should be described, demonstrating that samples chosen represent the entire batch.**

The sampling plan is included in the stability protocol in section 2.0 of Stability Summary and Conclusion of this submission.

- 28.h. The suppliers of the container-closure components (used for the stability studies which are reported in the NDA) should be indicated. It should be clarified whether these are identical to the container-closure components intended for marketing (except for the glass vial, _____, which is modified in your amendment dated 9/20/1991). The Lederle Packaging Code Number for the "aluminum flip cap seals" used in manufacture of drug product for the ongoing stability studies should be provided.**

b(4)

The suppliers of the components of the stability batches are included in section 2.0 of Container Closure System section of this submission.

- 28.i. You should clarify the meaning of the "bulk drug purity check" numbers (e.g., page 110, vol. 5).**

It is not applicable in this filing.

- 28.j. Stability data for drug product packaged in the new proposed vial _____ of 9/20/1991 amendment) should be provided to show that _____ of the vial (pg. 19 of amendment) does not adversely affect product stability.**

b(4)

It is not applicable in this filing. Also, we did not use vials treated with _____ during the manufacture of our product.

- 29. The remarks indicated below are with respect to your report on reconstitution compatibility and stability of the drug product (beginning on page 257, vol. 5).**

- 29.a. Appropriate stability data should be provided to support microbiological stability of reconstituted solutions in various media and containers. See additional labeling comments (below).**

A "reconstitution study" of l-leucovorin calcium for injection with 0.9% sodium chloride has been performed on 6-month stability samples stored at 25°C±2°C/60%±5% RH. Since from the start of reconstitution, through the admixture and to the end of infusion, takes less than 24 hours, no microbiology testing was performed.

- 29.b. It should be clarified where lot 0116-108A was manufactured (this lot was used for the reconstitution compatibility study, pg. 257, vol. 5), and whether the formulation used is identical to that proposed for marketing.**

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It is not applicable in this submission. We manufactured new drug product batches.

29.c. Analytical methods used for the reconstitution study should be specified.

A "reconstitution study" of l-leucovorin calcium for injection with 0.9% sodium chloride has been performed on 6-month stability samples stored at 25°C±2°C/60% ±5% RH. The corresponding analytical methods are included in the Reconstitution Study Protocol of the stability summary and conclusion section of this submission.

30. The following preliminary comments are concerned with the drug product labeling.

30.a. The comments below pertain to the "Dosage and Administration" section of the package insert.

30.a (1) Evidence of the microbiological stability of drug product reconstituted with _____ for injection should be provided to support the statement that such solutions are _____. Alternatively, such statements should be deleted.

b(4)

The new package insert does not specify the drug product to be reconstituted with _____

30.a.(2) A storage temperature should be provided to go with the statement that _____

_____ If the storage temperature includes room temperature, microbiological data should be provided to support this statement.

b(4)

_____, no microbiology testing was performed.

b(4)

30.a.(3) The statement concerning further dilution of reconstituted solutions of the drug product with 0.9% sodium chloride injection, USP and 5% dextrose injection, USP, which _____

b(4)

_____ should be modified as follows. Omit the chemical and physical storage information, which may be misleading in view of the possibility that storage times may be much shorter due to microbiological considerations, and in view of chemical changes in the drug product on dilution and storage in IV. Bags and tubing.

A compatibility study was performed using the reconstituted l-leucovorin calcium for injection in 0.9% sodium chloride and 5% dextrose. The results of this study are included in the "compatibility study report" in the stability data section of this submission.

30.a. (4) The sentence beginning with " _____ should be replaced by recommended storage _____"

b(4)

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times and conditions for constitution or dilution with various unpreserved vehicles, based on actual microbiological, physical and chemical data.

The package insert has been revised to state that _____

b(4)

30.b. Concerning the "How supplied" section of the package insert, the type of container (e.g., _____ vials) should be included.

The package insert has the appropriate information.

30.c. Labeling should clearly indicate that this product requires only half as much of the labeled active ingredient (by weight) per dose as the currently marketed leucovorin calcium for injection.

The Container and Carton and package insert labeling have been revised accordingly to indicate that this product requires only half as much of the labeled active ingredient.

30.d. Labeling should clearly indicate that the label claim of this drug product is calculated as _____

The Container and Carton labeling and package insert have been updated to indicate that the product is calculated as _____

b(4)

30.e. We recommend that the description section of the package insert also include the molecular formula for the active ingredient.

The Description section of the package insert is updated to include the molecular formula for the active ingredient.

30.f. You should contact USAN Council concerning the established name for the active ingredient. The name chosen by USAN (established name) should be used in all labels and labeling and it should be placed in parentheses between the trademark and the dosage form: e.g., Isovorin (levoleucovorin calcium) for Injection.

The USAN of the active ingredient has been established as levoleucovorin calcium as published in the Pharmacopeial Forum, Volume 18, Number 1, pp. 2980, Jan-Feb. 1992. An appropriate name has been in the current NDA filing. As per your recommendation, we have selected ISO-Vorin (levoleucovorin calcium) for Injection as the drug product name.

NDA 20-141

SUBMISSION DATES: December 14, 1990
June 20, 1991

L-LEUCOVORIN

LEDERLE LABORATORIES

b(4)

— 50, — mg IV vials

TYPE OF SUBMISSION: NME

REVIEWER: Suresh Mallikaarjun, Ph.D.

RECOMMENDATION:

1) The 5-methyl tetrahydrofolic acid (MTHF) AUC(0-24), AUC(0-∞), Cmax and Tmax of all the L-leucovorin tablets studied can be considered to be equivalent to the corresponding D,L-leucovorin tablets.

2) The MTHF AUC(0-24) and AUC (0-∞) of the L-leucovorin injection are equivalent to the corresponding AUCs of the D,L-leucovorin injection. However, the MTHF Cmax of the L-Leucovorin injection is significantly lower, and the Tmax later than the corresponding D,L-leucovorin injection.

If the Division of Oncology and Pulmonary Drug Products determines that these differences in the Cmax and Tmax of 5-methyl THF from the injection are not clinically significant, the Division of Biopharmaceutics will have no objection to the approval of the NDA, provided the labeling is amended to reflect these differences.

Please convey Comment 1 to the sponsor.

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Appendix II:

Note: Appendix II contains more detailed data/information such as dosage formulation, individual subject data and statistical analyses. This information is being retained in the Division of Biopharmaceutics, and can be obtained upon request.

BACKGROUND: The sponsor has an approved NDA (18-459) for D,L-leucovorin tablets and injection (NDA 08-107), and is now proposing to market the active l-isomer of leucovorin in the tablet and injection form. The dosing recommendation for the l-leucovorin tablets and injection is exactly half of that for the D,L leucovorin tablets and injection. The l-isomer is the active isomer and is metabolized to 5-methyl tetrahydrofolic acid (MTHF). The D-isomer is inactive, not metabolized, and is excreted unchanged in the urine.

The sponsor has conducted studies to show bioequivalence of MTHF pharmacokinetic parameters between L-leucovorin tablets and injection, and the D,L-leucovorin tablets and injection. Six studies have been submitted, of which two will not be reviewed since they were pilot bioavailability studies conducted _____ which are not proposed to be marketed by the sponsor.

b(4)

The highest tablet strength, 12.5 mg and the lowest strength 2.5 mg were studied as a 1 X 12.5 mg and 5 X 2.5 mg doses respectively, in study 76-4-1. The 7.5 mg tablets has been studied in dose proportionality study 76-3-1. Another dose proportionality study (76-17-1) linked the 2.5 mg, 7.5 mg and the 12.5 mg l-leucovorin tablets. Finally, dissolution profiles of _____ were submitted, which linked all the strengths. In an Oncology Drugs Advisory Committee meeting on 7/1/91, the committee voted 6-2 to approve l-leucovorin tablets and injection.

b(4)

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS:

The key results are based on the measurement in plasma by RIA of the active metabolite of l-leucovorin, 5-methyl tetrahydrofolic acid (MTHF), which is the major metabolite of l-leucovorin, and is the active moiety. The sponsor also measured total folates by a microbiological method. The total folate levels can be affected by a number of factors and the results are not as reliable as that from the MTHF data. The total folate results were not reviewed, but are provided in this review on request by the medical reviewer.

I. BIOAVAILABILITY/BIOEQUIVALENCE:

Absolute Bioavailability: The mean absolute bioavailability of the 2 X 7.5 mg tablet was approximately 74% as compared to the 7.5 mg IV dose. A decrease in the bioavailability with increasing oral doses has been shown earlier (NDA 18-459) with the D,L tablets and has been demonstrated in this NDA with the L-formulation; bioavailability of a 22.5 mg dose is 72%, and of 30 mg is 37%.

Bioequivalence:

The 90% confidence intervals (C.I.s) reported by the sponsor were verified by the reviewer and found to be correct.

Tablets:

b(4)

b(4)

Injection:

RIA method: The two one-sided test showed that the AUC, of the L-leucovorin (LL) injection (15 mg) was equivalent to the D,L-leucovorin (DLL) injection (30 mg). The same test indicated that the C_{max} of the LL injection was significantly lower (77.9 - 90.7), and the T_{max} significantly later (126.2 - 193.1) than the DLL injection (mean difference C_{max} -16%, T_{max} - 60%).

Microbiological method: The results were different from the RIA data. The two one-sided test showed that the area under the curve (AUC), of the L-leucovorin injection (7.5 mg) was lower (by approximately 16%) than the DLL injection (15 mg). The same test indicated that the C_{max} of the 7.5 mg LL injection was equivalent to the C_{max} of the 15 mg DLL injection. The T_{max} of the LL injection was later than the DLL injection (-8.6 - 241.9).

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 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

The accuracy was approximately greater than 90%, the intra-day variability (C.V.) was less than 10%, and the inter-day variability (C.V.) generally was less than 15%.

Linearity: Linear between 1 ng/ml to 20 ng/ml.

Sensitivity: L.O.Q. - 1 ng/ml.

Specificity: Cross reactivity with leucovorin was \approx 4 %.

GENERAL COMMENTS (Need not be sent to the firm):

b(4)

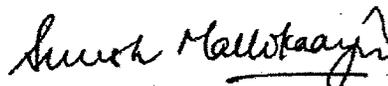
B) The Division of Biometrics examined the sponsor's factorial analysis to determine bioequivalence in Study 76-4-1 and concluded that the analysis is valid only if the sponsor had made certain assumptions *a priori*. However, due to reasons in Comment 1, the factorial analysis is moot, and the factorial analysis does not need to be considered for bioequivalence.

Labeling Comments:

C). The 5-MTHF Cmax and Tmax differences between the L- and D,L- injection should be included in the labeling.

COMMENTS TO BE SENT TO THE FIRM:

b(4)



Suresh Mallikaarjun, Ph.D.

FT initialed by John Hunt 7/26/91

cc: NDA 20-141, HFD-150, HFD-426 (Mallikaarjun, Hunt), Chron, Drug, Reviewer, FOI (HFD-19).

+ NDA 20-140
DIV FILE
HFD-150/A Justice
HFD-150/P Zimmerman

-5-

APPENDIX I

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 Draft Labeling (b5)

 Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**

/s/

Sophia Abraham
12/10/2007 11:48:53 AM
BIOPHARMACEUTICS

Brian Booth
1/3/2008 01:12:26 PM
BIOPHARMACEUTICS

**AMENDMENT
CLINICAL PHARMACOLOGY REVIEW**

NDA: 20-140
BRAND NAME: ISO-Vorin™
GENERIC NAME: /-Leucovorin Calcium
DOSAGE FORM: 50 mg Vials for Intravenous Injection
INDICATIONS: Rescue Therapy after High Dose Methotrexate Therapy
SUBMISSION DATE: 29-Jun-2007
SUBMISSION TYPE: NDA-Amendment
APPLICANT: Spectrum Pharmaceuticals
DDOP: Division of Drug Oncology Products
OCP DIVISION: Division of Clinical Pharmacology 5
OCP REVIEWER: Sophia Abraham, Ph.D.
OCP TEAM LEADER: Brian Booth, Ph.D.

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1. EXECUTIVE SUMMARY

This is an amendment to the previous review for NDA 20-140 submission of 29-Jun-2007 to address some of the FDA issues regarding the PLR labeling for ISO-Vorin™ (*l*-leucovorin calcium) for Injection. The final FDA revised labeling is presented in Appendix 1.

In response to the FDA issues, the sponsor submitted some published articles via an email on 29-Jan-2008 (see Appendix 2). Based on these published articles, the following labeling statement under Section 7 (Drug Interactions) of the PLR labeling:

“Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children.”

has been confirmed and modified to the following statement:

“Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children. It is not known whether folinic acid has the same effects. However, both folic and folinic acids share some common metabolic pathways. Caution should be taken when taking folinic acid in combination with anticonvulsant drugs.”

1.1 RECOMMENDATION

No action is indicated.

1.2 PHASE 4 COMMITMENTS

[None]

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

2 QUESTION BASED REVIEW

2.1 *General Attributes of the Drug*

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

2.1.3 What are the proposed dosage(s) and route(s) of administration?

2.2 *General clinical pharmacology*

2.2.1 What are the design features of the clinical studies used to support dosing or claims?

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD) and how are they measured in clinical pharmacology and clinical studies?

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

- 2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?
- 2.2.4.3 Does this drug prolong the QT or QTc interval?
- 2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?
- 2.2.5 What are the PK characteristics of the drug and its major metabolite?
 - 2.2.5.1 What are the single dose and multiple dose PK parameters?
 - 2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
 - 2.2.5.3 What are the characteristics of drug absorption?
 - 2.2.5.4 What are the characteristics of drug distribution?
 - 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?
 - 2.2.5.6 What are the characteristics of drug metabolism?
 - 2.2.5.7 What are the characteristics of drug excretion?
 - 2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?
 - 2.2.5.9 How do the PK parameters change with time following chronic dosing?
 - 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

2.3 *Intrinsic Factors*

- 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?
- 2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?
 - 2.3.2.1 Elderly
 - 2.3.2.2 Pediatric patients
 - 2.3.2.3 Gender
 - 2.3.2.4 Race
 - 2.3.2.5 Renal impairment
 - 2.3.2.6 Hepatic impairment
 - 2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?
 - 2.3.2.7 What pregnancy and lactation use information is there in the application?

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

General Biopharmaceutics

[NOT APPLICABLE]

2.5 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

2.6.2 Which metabolites have been selected for analysis and why?

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

2.6.4.2 What are the lower and upper limits of quantification (LLOQ)?

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

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X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Appendix 2. Published Articles

From: Cynthia Letizia [mailto:CLetizia@spectrumpharm.com]
Sent: Tuesday, January 29, 2008 12:51 PM
To: Zimmerman, Paul F
Subject: RE: NDA 20-140 for Isovorin - label - information request for anticonvulsant interaction statement

Dear Paul,

With reference to the abstracts sent in the email response of January 17, 2008, the citations and PubMed search results are provided herein. These will be included in a forthcoming eCTD-NDA amendment.

Please let me know if there are additional questions on this or any other aspect of the proposed labeling.

Regards,

Cynthia

From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Thursday, January 17, 2008 5:35 AM
To: Cynthia Letizia; John Spoden
Subject: NDA 20-140 for Isovorin - label

Dear Cynthia,

The DRUG INTERACTIONS section of the proposed Isovorin label states, "Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children."

Please provide evidence that **folinic acid may counteract the antiepileptic effect of drugs.**

Thanks
Paul

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/s/

Sophia Abraham
2/20/2008 11:06:36 AM
BIOPHARMACEUTICS

Brian Booth
2/20/2008 12:00:41 PM
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