

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-140

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 4, 2008
From	Ravi S. Harapanhalli, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	20-140
Applicant	Spectrum Pharmaceuticals, Inc.
Date of Submission	July 10, 2007 (Resubmission)
PDUFA Goal Date	3-7-08 (Réguler Clock)
Proprietary Name / Established (USAN) names	— Levoleucovorin) for Injection
Dosage forms / Strength	INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION for INTRAVENOUS USE
Proposed Indication(s)	<ol style="list-style-type: none"> 1. — rescue is indicated after high-dose methotrexate therapy in osteosarcoma. (1) 2. — is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists. (1) <p><u>Limitations of Use</u></p> <p>— is not approved for pernicious anemia and megaloblastic anemias. Improper use may cause a hematologic remission while neurologic manifestations continue to progress. (1.1)</p>
Recommended:	Approval

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1. Introduction

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. Most of these deficiencies were related to 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. It should be noted that the trade name ISO-Vorin was not accepted, instead, an alternate trade name — ” or — will be accepted during this review.

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This CTDL memo serves to highlight the critical approvability issues discussed in all review disciplines and makes an overall recommendation of “approval” for this NDA. All review disciplines have recommended approval of the NDA. Individual discipline reviews may be found in the DFS. Similarly, all disciplines have provided recommendations on labels and labeling. The labeling comments from DDMAC, DMETs, and SEALD were harmonized with the CMC comments and were addressed by the applicant. Final container/carton labels and Physician’s Package Insert have been provided that conform to

the recommendations made by the Agency. An expiration dating period of 24 months is grantable. This information should be included in the letter along with the agreed upon statement on CMC post-marketing commitment.

2. Background

Although *levoleucovorin* calcium (*l*-leucovorin) is not marketed in the United States (US), leucovorin calcium, as a racemic mixture (*d*-, *l*-leucovorin calcium), is available commercially both for parenteral use and as oral tablets. The racemic mixture is a 1:1 mixture of “*d*” and “*l*” forms but only the “*l*” form is pharmacologically active. Therefore, the recommended dose range for the pure *l*-isomeric form (ISO-vorin) is 50% of the dose range for the racemic mixture marketed in the US. *Leucovorin* calcium injection is marketed by Hospira (NDA #008107) and under several generic labels in the US. Leucovorin calcium tablets are marketed by Xanodyne Pharmacal (NDA #018459) and under several generic labels in the US. In Europe, *levoleucovorin* calcium (also known as calcium levofolinate) is marketed by multiple companies, including under the trade name ISO-Vorin by Wyeth in Spain, United Kingdom (UK) and France. Schering markets *l*-leucovorin calcium as Folanemin/Levofolene in Italy.

There are no important issues with pharmacologically related products. However, it should be noted that the dosing for *levoleucovorin* calcium is half that for the racemic mixture (*d,l*-leucovorin calcium) marketed in the US since 1952. Spectrum has proposed a Risk Management Plan to reduce the potential for dosing errors. FDA has recommended that the applicant not use ISO-vorin as the proprietary name in order to reduce product confusion and dosing errors.

The pre-submission regulatory history for this NDA is tabulated below.

12/14/1990	NDA 20-140 submitted to FDA by Lederle.
12/18/1990	FDA approved orphan drug status in the treatment of advanced metastatic colorectal adenocarcinoma in combination with 5-fluorouracil. (Application #90-485)
07/01/1991	ODAC voted 6-2 that ISO-Vorin is safe and effective for high dose methotrexate (MTX) rescue.
08/01/1991	FDA approved orphan drug status for use in conjunction with high dose MTX in the treatment of osteosarcoma. (Application #90-484)

01/03/1992	FDA issued Not Approvable (NA) letter (for injection _____) due to CMC and labeling deficiencies.	b(4)
01/9/1993	Lederle notified FDA of intent to Amend NDA 20-140 _____	
01/22/1993	Lederle submitted letter to FDA regarding deficiencies.	
12/13/1993	FDA issued NA letter to Lederle citing CMC deficiencies.	
04/22/1998	Following purchase of Lederle by Wyeth Pharmaceuticals, Lederle withdrew _____, and US rights reverted to Merck Eprova AG (Switzerland).	
12/04/2003	Merck Eprova licensed US rights for <i>l</i> -leucovorin products to Targent, Inc.	
11/29/2004	Letter of authorization provided from Merck Eprova to FDA for right of Targent to reference _____ and NDAs 20-140 and 20-141.	b(4)
07/18/2005	Pre-NDA meeting canceled by Targent, following review of FDA's written responses to sponsor's questions. FDA agreed the NDA resubmission would include a new CMC section, revised labeling, and a safety update. FDA also advised Targent to propose a Risk Management Plan to reduce the potential for dosing errors.	
04/19/2006	NDA ownership transferred from Targent to Spectrum.	
06/29/2007	Spectrum submitted Amendment to NDA 20-140 to FDA.	

Dosing Regimen and Administration

The proposed dosing regimen is 7.5 mg (approximately 5 mg/m²) intravenously every 6 hours for 10 doses starting 24 hours after beginning methotrexate infusion (based on a methotrexate dose of 12 gm/m² IV over 4 hours). Since only the "l" isomer of leucovorin is pharmacologically active, levoleucovorin is dosed at one-half the usual dose of the racemic mixture, *d,l*-leucovorin. Serum creatinine and methotrexate levels are to be measured daily and levoleucovorin, hydration and urinary alkalinization are to be continued until the methotrexate level is below 5 x 10⁻⁸ M (0.05 micromolar). For delayed methotrexate elimination and/or evidence of acute renal injury, the dose of levoleucovorin should be adjusted.

3. CMC/Device

On January 3, 1992, and December 13, 1993, FDA issued Not Approvable letters for the NDA, citing CMC deficiencies. The current resubmission (Amendment to NDA 20-140) contained responses to the cited deficiencies. The CMC primary reviewers Dr. Mark Sassaman (drug substance) and Dr. Sarah Pope (drug product) placed their review into DFS on March 3, 2008. All approvability issues to date have been resolved and there are no unresolved CMC issues.

3.1 General product quality considerations

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

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50 mg/vial.

The final product has a label claim of

Based on the dosage and administration section of the PI, it appears that maximum daily dose (MDD) for the drug could be 75 mg every 3 hours times eight, which comes to 600 mg. ICH Q3BR indicates a reporting threshold of — and a specification/ID/qualification threshold of — It can be seen that all specified impurities (identified and unidentified) are proposed at levels above the qualification thresholds. A discussion with the Pharmacology/Toxicology discipline concerning acceptability of the proposed levels was conducted on 26-FEB-2008. The Applicant referenced a preclinical attachment included in the 23-OCT-2007 amendment. This attachment was also discussed with the Pharmacology/Toxicology reviewer, as the Applicant argued that the provided preclinical data supported the proposed (revised) acceptance criteria for impurities. In an email dated 27-FEB-2008, the Pharm/Tox disciplines concurred with extrapolation of the preclinical data to support the proposed acceptance criteria (see email attachment at end of document).

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During the teleconference, the applicant made reference to their 12 months stability data and indicated that the data was within the above proposed interim limits for the degradation products and that they were in the process of submitting the 12 months stability update. The applicant also stated that the proposed limits are justified based on the above mentioned preclinical amendment to the NDA. However, the Pharmacology/Toxicology reviewer was unaware of the amendment and could not confirm immediately whether he concurred with the applicant's assertion. In view of this situation, during the telecom I agreed with the applicant that they should submit a quick stability update summary along with statistical analysis of stability data on degradation products and a justification for the proposed interim limits based on their reference to the preclinical studies carried out earlier. In his e-mail dated February 27, 2008, the Pharmacology/Toxicology reviewer, Hans Rosenfeldt indicated that from his perspective, the extrapolation data provided in the preclinical amendment dated 23-OCT-2007 in support of the proposed interim specifications for the impurities and degradation products was acceptable. Therefore, the following revised specifications for the drug product impurities were accepted.

Impurity	Originally Proposed	Revised 2/25/08
_____	_____	_____

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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 (email). Together, these updates included 12 months of long term and 6 months of accelerated stability data and statistical analysis of all stability-indicating quality attributes. No variation in trending was noted for any of the previously-reviewed attributes. Based on the application of ICH Q1E guidelines, a 24 months shelf life is grantable to this product when stored at room temperature.

3.2 CMC Microbiology:

The product quality microbiology review was placed into DFS by Dr. Robert Mello on February 20, 2008. He recommended approval of the NDA and did not identify any post-marketing comments. The following are the excerpts from his review.

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Appropriate data to support the microbial process validation have been provided in the NDA and there are no concerns with the use of _____ in the manufacture of the drug product. Similarly, the proposed limits for endotoxins and the sterility specifications are acceptable. It is also acceptable to have container closure integrity testing carried out at time zero and at expiry on the first three production lots. However, sterility and endotoxins will be tested at release and at 24 months expiry on a routine basis and this is acceptable.

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Based on the data on microbial challenge studies, because of uncertainties over growth characteristics, the data did not support an _____ post constitution hold time.

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Significant growth for *P. aeruginosa* started between the 12 and 18 hour time periods, not observed with the 0.9% saline controls. Based on the data, Dr. Mello required a hold time of not more than 12 hours following reconstitution of the drug product and further dilution with 0.9% saline. Since no data were provided for dilution with 5% Dextrose Injection, according to Dr. Mello, such dilutions may be held for not more than 4 hours. These were properly reflected in the revised package insert and on carton and container labels.

3.3 Facilities review/inspection

All facilities inspections have been completed. On February 14, 2008, the Offices of Compliance and New Drug Quality Assessment determined these facilities to be acceptable.

3.4 Other notable issues (resolved or outstanding)

There was a discussion on the chemical type and the filing category during the team meetings. The CMC reviewers were recommending that the drug be classified as a new molecular entity and that the date of approval on the PI be the date of approval of this NDA. However, the draft MaPP # 7500.3 entitled "Chemical Classification" describes "Type 5-New Formulation or New Manufacture, Same or New Indication" to include pure stereoisomer when the racemic mixture has been previously approved or marketed, and vice versa. So, in my opinion, Levoleucovorin should be classified as a Type 5 chemical entity rather than as an NME. Also, since the indication sought is the same as the one approved for the racemate, the initial date of approval on the PI should be the year of approval of the racemate leucovorin, which is 1952. The SEALD team originally recommended the same initial date of approval. Therefore, based on this discussion, the team made a decision that the chemical classification is Type 5 and the initial date of approval is 1952. However, in a teleconference, the firm objected to the initial date of approval and referenced Federal Register Notice (Vol. 71, No. 15, page 3937), which is excerpted below.

"The Agency is therefore limiting identification of the initial date of U.S. approval to new molecular entities, new biological products, or new combinations of active ingredients because this is sufficient to accomplish the goals of increasing prescriber vigilance and reporting of suspected adverse reactions when using newer products.....Although the Agency does not subscribe to the view that newer drugs are inherently less safe, it does believe that alerting a practitioner to the fact that a drug has been marketed for an extended period could provide some added assurance about the drug's safety margin based on cumulative, safe experience with the product."

Therefore, the firm argued that this product has never been approved for use in the U.S.. That, if the approval date is given as 1952, this will mislead physicians into thinking that this product has been used in the U.S. for over 50 years. That this may influence reporting of unexpected and serious adverse reactions and may distract the prescriber from the dosing recommendations which emphasize that levoleucovorin is dosed at half the usual dose of racemic leucovorin. During the teleconference, the team

clarified that levoleucovorin is not an NME because of the reasoning described above. Also, the proposed indications are same as for the racemic leucovorin and adequate caution is placed in the PI and on the labels to reflect that levoleucovorin should be dosed one half that of racemic leucovorin. Therefore, the team asked the firm to retain the initial date of approval as "1952 (*d,l*-leucovorin). The firm counter-proposed to keep this date and also to list the date of approval "2008 (*l*-leucovorin" and the team agreed with this compromise.

The review team discussed at length, whether the NDA filing category is 505(b) (1) as claimed by the applicant or it should be 505(b) (2) because of references to the literature and other sources to which the applicant does not have a right of reference. So, each discipline was asked to find out whether the applicant relied on published literature to support the proposed approval. If the published literature was required for approval, it was also important to determine whether the applicant made reference to such required literature or not. The clinical reviewer, Dr. Nancy Scher presented the following perspective on this issue in her e-mail dated January 29, 2008:

Their application says 505(b)(1) and I believe that is correct. Based on previous agreements between FDA and Lederle, the requirements for approval were as follows, as presented by Dr. Justice at the 1991 ODAC.

- *To provide evidence that the d-isomer did not contribute significantly to the efficacy of leucovorin rescue*
- *To demonstrate that the new products were bioequivalent for l-leucovorin*
- *To provide clinical evidence that the products could provide effective rescue after therapy with high dose methotrexate. However, FDA agreed a large randomized trial comparing rescue with l- and d,l-leucovorin would not be required if the first 2 conditions were satisfied.*

So, approval to be based on clinical pharmacology data and on limited clinical trial data of efficacy.

I asked for references from the literature, because the long-term use in Europe may be considered confirmatory to a limited clinical trial package. This was not part of the FDA requirement, with which ODAC agreed in 1991.

The pharmacology/toxicology reviewer Hans Rosenfeldt, in his e-mail dated January 29, 2008 presented the following view.

"From the pharm/tox perspective, we are using literature only to verify assertions that were made in the original racemic leucovorin label."

The clinical pharmacology reviewer, Dr. Sophia Abraham, in her e-mail dated January 29, 2008 provided the following statement.

"I used literature to verify the "Drug Interaction" and "Pharmacodynamics" sections."

I provided the following view from CMC perspective in my e-mail dated January 29, 2008.

CMC is a stand alone package and is not relying on published literature. Also, the CMC review and a decision on approval recommendation are based on the data submitted in the NDA/DMFs and not based on any literature data.

Thus, based on the overall assessment from various disciplines, a decision was made that this NDA is a 505 (b) (2) application.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Hans Rosenfeldt recommended approval of the NDA from his perspective and placed his review in DFS on February 27, 2008. He made reference to the original pharmacology/toxicology review by Dr. A. W. Coulter, and summarized the original review findings in his current review and recommended approval of the NDA.

The sponsor submitted toxicology studies in mice, rats, and dogs with the original submission of this NDA. Overall, these studies indicated that levoleucovorin was less toxic than *dl*-leucovorin. At high doses, levoleucovorin caused sedation, rapid breathing, tremors, convulsions and death in mice and rats. No mortalities were observed at doses given to dogs and the only clinical sign observed in this study was a slightly increased emesis in dogs treated with high-dose levoleucovorin or *dl*-leucovorin.

A discussion on pharmacological activity revealed that levoleucovorin is converted to 5-methyltetrahydrofolate (5-MeTHF) *in vivo*. 5-MeTHF is readily converted to tetrahydrofolic acid (THF) by 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), where it can participate in thymidylate synthesis and other metabolic processes as a single carbon donor. The conversion of levoleucovorin to THF bypasses the inhibition of dihydrofolate reductase by methotrexate and rescues DNA metabolism from the effects of this drug. Thus, the pharmacologic activity of levoleucovorin is consistent with the proposed indications of co-administration of levoleucovorin with high-dose methotrexate in the treatment of osteosarcoma and treatment of accidental methotrexate overdoses.

Nonclinical safety issues relevant to clinical use were summarized as follows. Nonclinical data submitted by the sponsor demonstrated that levoleucovorin is the pharmacologically active diastereoisomer of *dl*-leucovorin, and that levoleucovorin is about twice as potent as *dl*-leucovorin in ameliorating the toxic effects of methotrexate. A pharmacokinetic study of levoleucovorin and *dl*-leucovorin in dogs showed that the half-life of levoleucovorin is three times shorter than *d*-leucovorin. This pharmacokinetic difference reflects the fact that levoleucovorin is readily metabolized and renally excreted while *d*-leucovorin cannot be metabolized and can only be excreted renally.

Current resubmission refers to teratology studies submitted under NDAs 8-107 and 18-459. These studies were performed with the tablet form of *dl*-leucovorin. Subsequent bioavailability studies show that the oral bioavailability of *dl*-leucovorin tablets at the

doses given in the referred teratology studies is 5-10%. Therefore, in the opinion of Dr. Rosenfeldt, these teratology studies are inadequate and cannot support a Pregnancy Category \ as proposed by the sponsor. Subsequently, the sponsor agreed to accept a Pregnancy Category C. Dr. Rosenfeldt also indicated that no new nonclinical studies are required for the approval of this NDA

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5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewer, Dr. Sophia Abraham recommended approval of the NDA in her review that was placed into DFS on January 3, 2008, and she did not identify any comments or post-marketing commitments. Study report entitled "Tablet bioequivalence study # 76-4-1" was attached at the end of her review. The objective of the study was to determine the BE of Lederle *l*-leuovorin 2.5 mg and 12.5 mg tablets compared to the commercially available Lederle *d,l*-leuovorin 5 mg and 25 mg tablets respectively. She concurred with the findings of the study report that the two products were bioequivalent. She also indicated that her review of the clinical pharmacology/pharmacokinetics section of the PLR focused on the correctness of content compared to the original labeling provided in the original NDA. Labeling information regarding _____ from the Pharmacokinetics subsection and no changes were made in the pharmacokinetics of leuovorin following the intravenous route. This is acceptable because, the dosage form in question is an injectable _____ The reviewer recommended the following revision to the clinical pharmacology section of the package insert. (12. Clinical Pharmacology, 12.3 Pharmacokinetics)

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"The pharmacokinetics of levoleuovorin 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 _____ 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 _____ was 5.1 and 6.8 hours, respectively."

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This revision was included in the package insert.

General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc., drug-drug interactions, pathway of elimination, intrinsic factors affecting elimination, demographic interactions/special populations, gender effects, QT assessments, etc. are not discussed in the clinical pharmacology review as this is covered in detail in the original review of 1990.

Drug-Drug Interactions: Drug-drug interactions were not studied during the development plan. There is evidence from the medical literature that 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, since folic and folinic acids share some common metabolic pathways, caution should be taken when administering folinic acid in combination with anticonvulsant drugs. Levoleuovorin increases the toxicity of 5-fluorouracil.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

The joint clinical/statistical review of the NDA resubmission was carried out by Dr. Nancy Scher and Dr. Shenghui Tang. They recommended the approval of this NDA, and did not identify any post-marketing commitments. Their joint review was placed in DFS on February 27, 2008.

Levoleucovorin calcium (*l*-leucovorin), also known as levofolinic acid, is a folate analog. It is the stereoisomer of *d,l*-leucovorin calcium, which has been licensed in the US since 1952. Only the "*l*" form of leucovorin is pharmacologically active. No new clinical trial data were submitted with this application. The following synopsis refers to the trial data submitted in 1991, which FDA determined, and the Oncologic Drugs Advisory Committee concurred, provided evidence of safety and efficacy for *l*-leucovorin for the indications.

Sources of clinical efficacy data submitted to NDA in 1990 are summarized below.

Protocols	Patient Number	Age Range in Years	Formulation <i>l</i> -Leucovorin	Dose <i>l</i> -Leucovorin	Methotrexate Regimen
POG	10	10-21	Tablets and IV	7.5 mg q6h x10 at 20 hours after end of HDM	12 g/m ² IV over 4 hours
TIOS-III	3	4-15	IV	7.5 mg q3h x18 at 12 hours after end of HDM	12.5 g/ m ² IV over 6 hours
OS-86	3	7-17	Tablets and IV	7.5 mg q6h x10 at 20 hours after end of HDM	12 g/m ² IV over 4 hours

Indication and population studied: Children and young adults ages 6-21 were treated with levoleucovorin, in the adjuvant and metastatic settings, following therapy with high-dose methotrexate (HDM) for osteosarcoma. The indications are:

- After high-dose methotrexate therapy in osteosarcoma
- To diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

Number of pivotal efficacy and safety trials: Patients were treated using (multidrug) regimens from 5 different pediatric trials for osteosarcoma, which included HDM as one component, and which utilized 3 different levoleucovorin rescue protocols. "Matched historical controls" treated with *d,l*-leucovorin were selected from the respective studies for comparison.

Number of patients enrolled in the primary trials: There were 16 patients with osteogenic sarcoma treated with levoleucovorin after 58 courses of HDM. There were 28 historical controls who received 101 courses of HDM followed by *d,l*-leucovorin rescue.

No new clinical trial data were provided for this submission. In 1991 the FDA Clinical Reviewers and the Oncological Drugs Advisory Committee determined that there were sufficient data to support the safety and efficacy of levoleucovorin for the proposed indications. The efficacy of levoleucovorin rescue following high-dose methotrexate was based on the demonstration that levoleucovorin prevented the severe toxicity certain to occur in the absence of adequate "rescue." Conclusions could not be made regarding the comparative efficacy of leucovorin and the historical controls treated with *d,l*-leucovorin due to the small number and low evaluability rate of the latter. Non Approvable letters were issued in 1992 and 1993 because of CMC deficiencies. As summarized in the CMC section, these issues are now resolved for the intravenous formulation of levoleucovorin.

8. Safety

Overall number of patients in the safety database and extent of exposure: There were 16 patients ages 6-21 who received 58 courses of HDM therapy for osteogenic sarcoma. The mean number of levoleucovorin doses per course was 18.2 and the mean total dose per course was 350 mg. The original sponsor, Lederle Laboratories, submitted a 120-day safety update to NDA 20-140 and 20-141 (levoleucovorin tablets) on May 16, 1991. The update provided data for 48 additional courses of therapy for 8 patients in the original study group, as well as data for 9 new patients treated with a total of 50 courses of therapy. Including all patients treated, the applicant reports that the mean number of doses of levoleucovorin per course is 15.8 and the mean total dose per course is 291 mg. For the new patients reported in the update, 6 patients were ages 10-19; 2 patients were younger than age 10, and 1 patient was age 20-29.

No new clinical trial data were provided for this submission. The efficacy of levoleucovorin rescue following high-dose methotrexate (HDM) was based on the demonstration that levoleucovorin prevented the severe toxicity known to occur in the absence of adequate "rescue." For the current submission, the applicant provided a safety update based on international post marketing experience for calcium levoleucovorin from the World Health Organization (WHO) Uppsala Post marketing database. The applicant submitted a review of the medical literature to provide additional support for safety. Although there were numerous reports of levoleucovorin in combination with 5-fluorouracil for colorectal carcinoma, the applicant was able to provide only three published studies reporting the use of levoleucovorin with HDM for osteosarcoma. No notable safety issues were encountered during this review.

9. Advisory Committee Meeting

The Oncologic Drugs Advisory Committee (ODEC) meeting was held on July 1, 1990 in which the committee voted 6-2 in favor of approval and stated that levoleucovorin is safe and effective for high dose methotrexate (MTX) rescue. During the same meeting, Dr. Justice laid out the following criteria for the approval of levoleucovorin.

- *To provide evidence that the d-isomer did not contribute significantly to the efficacy of leucovorin rescue*
- *To demonstrate that the new products were bioequivalent for l-leucovorin*
- *To provide clinical evidence that the products could provide effective rescue after therapy with high dose methotrexate. However, FDA agreed a large randomized trial comparing rescue with l- and d,l-leucovorin would not be required if the first 2 conditions were satisfied.*

10. Pediatrics, Geriatrics, and Special Population

There are no special dosing considerations identified for race, gender, age for adults or for children. Clinical studies of levoleucovorin in the treatment of osteosarcoma evaluated a pediatric population, and did not include subjects aged 65 and over to determine whether they respond differently from younger subjects.

There have been no studies done with regard to dose modifications for hepatic or renal insufficiency. No dosing modifications would be anticipated for the proposed indication.

Animal reproduction studies have not been conducted with levoleucovorin. It is also not known whether levoleucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Levoleucovorin should be given to a pregnant woman only if clearly needed and is classified Pregnancy Category C.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when levoleucovorin is administered to a nursing mother

11. Other Relevant Regulatory Issues

- *Application Integrity Policy (AIP): This was not raised during the pre-approval inspections for this NDA.*
- *Exclusivity or patent issues of concern: No issues pertaining to exclusivity or patents were noted for this NDA.*
- *Financial disclosures: N/A*
- *Other GCP issues: N/A*
- *DSI audits: N/A*
- *Other discipline consults: Product quality microbiology recommended approval.*
- *Any other outstanding regulatory issues: None*

12. Labeling

Highlights of labeling discussions and areas of concern and their resolution have been described below. Since revisions to the labels and labeling were made subsequent to the placement of the primary CMC review, the new information is also discussed here and the most updated carton and container labels are attached.

12.1 Proprietary name:

The applicant has proposed two trade names, namely, DDMAC review indicates that they have no objection to the use of either of these names. However, DMETs has not yet made a decision on the acceptability. In the mean time, the applicant was asked to revise the package insert with a place holder "Tradename" and to submit the container and carton labels with three names, "Tradename", ''. All the revised labels from March 3, 2008 communication were reviewed and were deemed adequate from DDMAC, and CMC perspective. However, feedback from DMETs is awaited.

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12.2 Established name:

Originally, the applicant proposed an established name that included (levoleucovorin calcium) for Injection. However, the product strength is based on the active moiety, levoleucovorin. The DMETs labeling review by Richard Abate, dated December 13, 2008 indicated that they brought up this apparent discrepancy with ONDQA reviewers and that we proposed the following name/strength nomenclature.

Iso-vorin (levoleucovorin calcium) for injection
Equivalent to levoleucovorin
50 mg

However, this nomenclature is not consistent with the recommendations of Labeling and Nomenclature Committee (LNC), which recommends that the strength should immediately follow the established name and that both should match. Also, upon discussion with the clinical discipline, it was apparent that because of potential safety concerns with product mix-up resulting from similarities in the nomenclature and format of labeling between levoleucovorin and the racemic leucovorin, they would prefer anything that makes this product look different from racemic leucovorin. The DMETs labeling review by Dr. Richard Abate also indicated that because of potential medication errors with the use of Iso-vorin with Leucovorin, they did not accept the originally proposed trade name, Iso-vorin. Therefore, in discussion with the Chair of the LNC, Dr. Rik Lostritto, the following revised established name was proposed by this reviewer and was accepted by the firm. Furthermore, the DMETs reviewer, Dr. Richard Abate also concurred with this nomenclature from their perspective.

Tradename (levoleucovorin) for injection
50 mg
(present as levoleucovorin calcium)

Accordingly, the package insert and the container and carton labels were revised to reflect this nomenclature.

12.3 DDMAC and DMETS comments:

DDMAC reviewer, JuWon Lee in her e-mail dated March 3, 2008 confirmed that the most recent updates to the package insert and the container and carton labels were acceptable to DDMAC. They also indicated that they have no issues with accepting either of the two proposed trade names. However, as discussed above, the DMETS feedback on the acceptability of the trade name and the revised container and carton labels is awaited as on the date of this review.

12.4 Physician labeling:

The physician package insert has been revised to include all recommendations from all disciplines. The latest PI is submitted to the NDA on March 3, 2008. There are no outstanding issues with the PI.

12.5 Issues not resolved at the time of completion of the CDTL review:

The DMETS has not made a decision on the acceptability of the proposed trade name. The originally proposed trade name "ISO-Vorin" was rejected. The firm proposed _____ and DMETS acceptability is awaited, although, an e-mail from the DMETS reviewer to the project manager, Paul Zimmerman indicates their acceptability of _____. Therefore, this memo assumes that _____ is the accepted trade name. An official memo from DMETS is expected before the PDUFA action date of March 7, 2008.

b(4)

12.6 Carton and immediate container labels:

Since, the dose equivalency statement on the container and carton labels was not consistent with that in the PI, the CMC reviewer recommended replacing "The recommended dose of Adjuncta is 7.5 mg, equivalent to 15 mg of racemic leucovorin" with "Present as the calcium salt equivalent to 50 mg levoleucovorin." However, this revised statement will not adequately caution the healthcare providers that the dose to be taken is one half that of racemic leucovorin. The clinical discipline concurred with this concern and upon discussion with Dr. Ann Farrell, the following revised statement was recommended in the labels.

"Levoleucovorin should be dosed at half that of racemic leucovorin"

On 29 FEB 2008, the following comments were conveyed to the applicant.

Please submit revised carton and container labels for the proposed trade names with the following recommendations.

Regarding the carton we have the following comments:

1. The prominence of the "Rx Only" statement needs to be increased.
2. The size and prominence of the established name needs to be at least one-half of the size and prominence of the proposed trade name.
3. Increase the size of the "present as levoleucovorin calcium" statement.
4. Replace " _____" with "Levoleucovorin should be dosed at half that of racemic leucovorin."

b(4)

Regarding the container label we have the following comments:

5. The size and prominence of the established name needs to be at least one-half of the size and prominence of the proposed trade name.

In response to the above comments, the applicant submitted the following revised container and carton labels on March 3, 2008. They were reviewed and were deemed acceptable from CMC and DDMAC perspective. All the above concerns were addressed in these revised labels. However, as on the date of this memo, DMETs has not determined the acceptability of the proposed trade names. Similarly, they have not yet commented on the acceptability of these revised labels.

b(4)

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

_____ in the SPL listing and stated that this is not in conformance with the SPL labeling format. In consultation with the LNC chair, Dr. Rik Lostritto, we agreed that if the firm cannot include this modifier, they should provide a justification and that will be acceptable.

b(4)

12.7 Patient labeling/Medication guide (if considered or required):

This is not required for this product.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action:

This reviewer recommends approval of this NDA. The reviews from all disciplines are in the DFS and all reviewers have recommended approval of this NDA. All outstanding approvability issues have been resolved and a CMC post-marketing commitment has been agreed to by the applicant.

13.2 Risk Benefit Assessment:

The approval of this NDA is based on clinical pharmacology data and on limited clinical trial data of efficacy. The applicant has provided evidence that the d-isomer did not contribute significantly to the efficacy of leucovorin rescue, and demonstrated the bioequivalence of l-leucovorin in _____ and racemic leucovorin. Since the FDA agreed during the 1991 ODAC that a large randomized trial comparing rescue with l- and d,l-leucovorin to demonstrate clinical evidence of effective rescue after therapy with high dose methotrexate would not be required if the above conditions were satisfied, this data was not submitted. Since the d-isomer is shown not to contribute to efficacy, and since the proposed medication dose for _____ is one half that of the racemic leucovorin approved earlier, the new product is expected to have a better risk benefit profile. However, this remains to be confirmed during post-marketing safety assessments following the approval of this NDA.

b(4)

13.3 Recommendation for Post marketing Risk Management Activities:

This NDA does not have any issues pertaining to restricted distribution, RiskMAPs, REMS. No special risk management activities have been recommended as of this time except for a change in proprietary name. The applicant submitted a Risk Management Plan to reduce the potential for dosing errors by using "tall man" lettering for the proprietary product name, ISOvorin, and enhancements to product labeling to avoid confusion with the currently marked racemic leucovorin products. FDA recommended against use of the name ISO-vorin and also against "tall man" lettering for the proprietary name. The applicant proposed the names _____ which are under review by DMETs. The use of either of the proposed proprietary name, should help avoid product confusion and resultant dosing errors..

b(4)

13.4 Recommendation for other Postmarketing Study Commitments:

During the teleconference dated February 25, 2008, the Agency brought to applicant's notice that — impurities listed in the drug product specifications have exceeded their identification thresholds and yet, their identity has not yet been established. Therefore, the firm was asked to provide a post-marketing commitment 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. It is acceptable to carry out this study post-approval because the chemical structures for these impurities have been tentatively worked out by the DMF holder. The NDA applicant is being asked to confirm the tentative structures within six months from the date of approval of this NDA. It should be noted that this PMC is a voluntary study and is not required under any of the regulatory provisions such as PREA, Subpart H, FDAA, and the study does not present significant safety issue. Therefore, the following voluntary PMC was agreed to between the Agency and the firm. In an amendment dated March 3, 2008, the firm submitted the following PMC.

b(4)

Study title: Establishing identity of the degradation products, _____ in the drug product specifications.

b(4)

Study submission date: Not needed

Study initiation date: Immediately

Submission of study report date: September 15, 2008

This should be included in the action letter.

13.5 Recommended Comments to Applicant:

The following comments should be included in the action letter.

An expiration dating period of 24 months is granted when the drug product is stored as recommended in the labeling. You may extend the expiration dating period upon accrual of real time stability data and report this in the next annual report.

You are reminded of your post-marketing commitment to establish the identities of _____ and to report the results by September 15, 2008.

b(4)

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

/s/

Ravi Harapanhalli
3/4/2008 06:45:25 PM
CHEMIST