CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-140

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	2/27/2008
From	Ann T. Farrell, M.D., Deputy Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	20140
Applicant Name	Spectrum Pharmaceuticals
Date of Submission	July 10, 2007
PDUFA Goal Date	Not under PDUFA (response to non-approval letter predating PDUFA)
Proprietary Name / Established (USAN) Name	levoleucovorin
Dosage Forms / Strength	Intravenous injection
Proposed Indication(s)	1. indicated for after high dose methotrexate therapy in osteosarcoma 2. indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Original 1991 medical officer review by Drs. Brett, Justice, and Johnson; Combined 2008 medical officer and stat review by Drs. Scher, Tang, Sridhara, and Farrell
Statistical Review	
Pharmacology Toxicology Review	Original 1991 review by Dr. Coulter; 2008 review by Drs. Hans Rosenfeldt and W. David McGuinn
CMC Review/OBP Review	Original 1991 review by Drs. Poochikian, Blumenstein, Leak, and Schroeder; 2008 review by Drs. Sarah Pope and Mark Sassaman
Microbiology Review	Original 1991 review by Dr. Peter Cooney; 2008 Review by Drs. Mello and Riley
Clinical Pharmacology Review	Original review by Dr. Mallikaarjun; 2008 reviews by Drs. Sophia Abraham and Brian Booth
DDMAC	Review by Dr. JuWon Lee
DSI	Not needed for this submission
CDTL Review	Review by Dr. Ravi Harapanhalli
OSE/DMEP	Review by Mr. Richard Abate R Ph, MS, Secondary

	Review by Dr. Kellie Taylor
OSE/DDRE	Verbal consultation with Dr. Scher (see her review)
OSE/DSRCS	Not needed
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

On December 14, 1990, Lederle Laboratories submitted an NDA for intravenous injection formulation for l-leucovorin for the following indication "Isovorin rescue is indicated for after high dose methotrexate therapy in osteosarcoma. Isovorin is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists." The Agency granted orphan drug status on August 1, 1991 for use in conjunction with high dose methotrexate in the treatment of osteosarcoma.

The company received a non-approval letter on January 3, 1992 outlining chemistry, manufacturing and control deficiencies. Spectrum Pharmaceuticals submitted their complete response to those deficiencies on July 10, 2007. Spectrum Pharmaceuticals supplemented their submission with a major chemistry amendment November 5, 2007 which extended the review clock.

The current submission consists of responses to the CMC deficiencies identified in the original review and updated safety information.

2. Background

Levoleucovorin calcium (*l*-leucovorin), also known as levofolinic acid, is a folate analog and 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. Levoleucovorin has been marketed since 1991 in Europe and since 1999 in Japan.

Originally Lederle submitted 2 NDAs for levoleucovorin. One NDA was for the intravenous injection formulation and the other was for a tablet formulation. These applications were not approved due to chemistry, manufacturing, and control deficiencies. The sponsor submitted

their complete response to deficiencies on July 10, 2007. A major chemistry amendment was submitted November 5, 2007 which extended the review clock. This application was submitted prior to PDUFA so PDUFA goals and other requirements do not apply.

The original non-approval letter was 25 pages long and contained only chemistry deficiencies. These deficiencies included:

Drug Substance (description, potential impurities, manufacturing process, assay specifications, lack of in-process testing, drug substance specifications, packaging, labeling, stability)

Drug Product (batch formulation, manufacturing, in-process testing, release testing, specifications, certificate of analysis issues, packaging, stability, compatibility, labeling)

3. CMC/Device

All prior outstanding CMC issues have been resolved.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months.

There are no outstanding issues that would interfere with approval. However the CMC review did uncover — drug product impurities listed in the drug product specifications have exceeded their identification thresholds and yet, their identity has not yet been established. Dr. Harapanhalli stated in his CDTL memo that, "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, ——— ———n the drug product specifications.

b(4)

Study submission date: Not needed
Study initiation date: Immediately
Submission of study report date: September 15, 2008"

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. Due to the fact that the clinical pharmacology/biopharmaceutics reviewer had to use literature for labeling, this application is considered a 505 (b) (2).

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The original NDA submission contained a clinical section to demonstrate the efficacy and safety of l-leucovorin. The clinical section contained l-leucovorin use data from several studies/databases which were compared with concurrent historical controls receiving *d,l*-leucovorin. The studies/databases that provided information on the use of l-leucovorin included: 1) Pediatric Oncology Group combined data on the use of l-leucovorin to rescue patients with osteosarcoma who received high-dose methotrexate from 3 pediatric group protocols (8759, 8651, and 8107), 2) TIOS-III Study which studied the use of l-leucovorin to rescue patients with osteosarcoma treated with a high dose methotrexate regimen according to an MD Anderson Cancer Center Protocol and 3) OS-86 Study which studied the use of l-leucovorin to rescue patients with osteosarcoma treated with a high dose methotrexate regimen according to a St. Jude Children's Hospital protocol. Efficacy was to be demonstrated by the effectiveness of l-leucovorin in preventing the severe toxicity expected following administration of high dose methotrexate in the absence of "rescue." The incidence and severity of toxicities were to be compared for the two treatment groups for leucopenia, thrombocytopenia, mucositis, and liver function abnormalities. The serum methotrexate level data was audited to ensure that patients received sufficiently high doses of methotrexate (MTX) necessitating treatment. Dr. Scher's review notes, "The data reflect that the intensity of MTX therapy was such that patients would have experienced severe toxicity in the absence of effective leucovorin rescue." From the original 1991 clinical review, "The submitted NDA should be approved, since l-leucovorin has been shown to prevent the expected severe toxicity of high-dose methotrexate."

The current clinical and statistical review teams agree with the original clinical review team and the July 1991 ODAC meeting that the use of l-leucovorin demonstrated efficacy (prevented toxicity) for high dose methotrexate rescue.

8. Safety

The original data base consisted of 16 patients ages 6-21 who received 58 courses of HDM therapy for osteosarcoma. The original sponsor, Lederle Laboratories, submitted a 120-day safety update to the NDA 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. Of the patients newly reported in the update 6 were ages 10-19, with 2 patients younger than age 10 and 1 patient age 20-29. The adverse reactions most frequently seen were vomiting, stomatitis, and nausea.

Levoleucovorin has been marketed since 1991 in Europe and since 1999 in Japan. Due to the foreign marketing, post-marketing safety data from the World Health Organization was available for review. The submission included an analysis of the World Health Organization (WHO) Uppsala international postmarketing safety data submitted by the sponsor. No new adverse reactions were reported in this database.

The primary reviewer conducted an independent review of the medical literature revealed two case reports of allergic reactions associated with folate analogs. Dr. Scher's review detailed the findings, "One well-documented report cited anaphylactic shock in a man due to IV folinic acid as part of a regimen of therapy with 5-fluorouracil, where other drugs were eliminated as the cause (Benchalal 2002). A second study demonstrated IgE-mediated anaphylaxis in a woman associated with oral ingestion of folic acid vitamin supplements. In the latter case, subsequent graded oral challenge with folinic acid (leucovorin) resulted in generalized urticaria, after 100 mg, but not after 10 or 50 mg (Dykewicz 2000)."

There are no clinical data regarding the potential adverse reactions resulting from an overdose. An overdose could potentially interfere with the efficacy of the chemotherapy.

No specific risk management plan is necessary for this drug except for labeling to avoid confusion with calcium d, l-leucovorin. Levoleucovorin is dose at one half of the racemic leucovorin.

9. Advisory Committee Meeting

This application was reviewed at an Oncologic Drugs Advisory Committee meeting on July 1, 1991. The committee voted in favor of approval (6-2) from the ODAC transcript, "the limited clinical data [were] sufficient to confirm that ISO-vorin injection is safe and effective when used in the rescue of high dose methotrexate."

10. Pediatrics

This pre-PDUFA application included data from pediatric patients and demonstrated the safe and effective use in children.

11. Other Relevant Regulatory Issues

The application is a 505 (b) (2) based on the fact that literature was required for labeling. Levoleucovorin has orphan drug status for use in conjunction with high dose methotrexate in the treatment of osteosarcoma. There are no other relevant regulatory issues.

12. Labeling

The approved labeling is in PLR format. During the review problems were identified with the proposed proprietary name, ISO-vorin, and the sponsor provided 2 alternatives. All issues regarding labeling including the package insert, carton, and immediate container labels are resolved except for the proprietary name.

The Division of Medical Error Prevention review team differed regarding the proposed name, —— Mr. Richard Abate in his review concluded, "The results of the Proprietary Name Risk Assessment found that the proposed name, —— , has some similarity to other proprietary and established drug names, but the findings of the FMEA indicates that —— does not appear to be vulnerable to name confusion that could lead to medication errors from a sound-alike/look-alike perspective." However, Dr. Kellie Taylor, his team leader in the Division of Medical Error Prevention stated, "Based on my analysis, I believe the orthographic similarity of the names —— and —— may result in medication errors in the usual practice setting. I recommend that the name, —— , not be approved for this product." The sponsor had submitted an alternative proprietary name, —— which will be reviewed post-action. b(4)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

Levoleucovorin is the l-isomer of the racemate approved in 1952. Levoleucovorin is the pharmacologically active isomer of leucovorin [(6-S)-leucovorin.] Levoleucovorin has been marketed in Europe since 1991 and Japan since 1999. The efficacy and safety profile of this product has been established. Review of the safety information submitted with the NDA and the clinical reviewer's search of the medical literature did not uncover any new or unexpected toxicity that was not seen with the racemic leucovorin. These levoleucovorin toxicities can be managed with appropriate labeling.

- Recommendation for Postmarketing Risk Management Activities

No specific risk management plan is necessary for this drug except for labeling to avoid confusion with calcium d, l-leucovorin. Levoleucovorin is dose at one half of the racemic leucovorin.

- Recommendation for other Postmarketing Study Commitments

Spectrum Pharmaceuticals has agreed to confirm the structural identity of the degradation products listed as —— in the drug product specifications within six months from the date of approval of the NDA. Spectrum Pharmaceuticals has agreed to submit this information in a new communication to the NDA prior to October 2008 and in the next annual report. b(4)

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/s/

Ann Farrell
3/7/2008 02:22:52 PM
MEDICAL OFFICER