CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211226Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 17, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 211226
Product Name and Strength:	Khapzory (levoleucovorin) for Injection, 175 mg/vial and 300 mg/vial
Applicant/Sponsor Name:	Spectrum Pharmaceuticals, Inc.
FDA Received Date:	October 16, 2018
OSE RCM #:	2018-552-2
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised container labels and carton labeling for Khapzory (Appendix A) to determine if they are acceptable from a medication error perspective. On October 16, 2018, Spectrum submitted revised container labels and carton labeling to include the recently approved proprietary name, Khapzory.[a]

2 CONCLUSION

The revised container labels and carton labeling for Khapzory are acceptable from a medication error perspective. We have no further recommendations at this time.

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[a] Little, C. Proprietary Name Review for Khapzory (NDA 211226). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 10. RCM No.: 2018- 25999491.

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/s/

COLLEEN L LITTLE
10/17/2018

SEVAN H KOLEJIAN
10/17/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 17, 2018

To: Autumn Zack-Taylor, Regulatory Project Manager, Division of Oncology Products 2 (DOP 2)

Stacy Shord, Associate Director for Labeling, DOP 2

From: Carole Broadnax, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for KHAPZORY (levoleucovorin) for injection, for intravenous use

NDA: 211226

In response to DOP 2's consult request dated January 24, 2018, OPDP provided initial comments on August 1, 2018, for proposed product labeling (PI) and carton and container labeling for the original NDA submission for BRAND NAME (levoleucovorin).

This addendum is for OPDP's review of revised draft carton and container labeling. The revised labeling includes the following changes:

1. Replaced "Brand Name (levoleucovorin) for injection" with the Khapzory logo on the vial and carton labeling for the 175 mg/vial and 300 mg/vial strengths.
2. Changed the color of the "175 mg/vial" text on the vial and carton labeling from (b) (4) to green.
3. Changed the color of the "300 mg/vial" text on the vial and carton labeling from (b) (4) to gold.
4. Deleted (b) (4) on the carton labeling for the 175 mg/vial and 300 mg/vial strengths.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DOP 2 (Autumn Zack-Taylor) on October 17, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at (301) 796-0575 or carole.broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
10/17/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 9, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 211226
Product Name and Strength:	Levoleucovorin for Injection, 175 mg/vial, and 300 mg/vial
Applicant/Sponsor Name:	Spectrum Pharmaceuticals, Inc.
FDA Received Date:	July 26, 2018
OSE RCM #:	2018-552-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised container labels and carton labeling for Levoleucovorin (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for Levoleucovorin is acceptable from a medication error perspective. We have no further recommendations at this time.

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[a] Little C. Label and Labeling Review for Levoleucovorin (NDA 211226). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 16. RCM No.: 2018-552.

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/s/

COLLEEN L LITTLE
08/09/2018

CHI-MING TU
08/09/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 1, 2018

To: Autumn Zack-Taylor, Regulatory Project Manager, Division of Oncology Products 2 (DOP 2)

Stacy Shord, Associate Director for Labeling, DOP 2

From: Carole Broadnax, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for BRAND NAME (levoleucovorin) for injection, for intravenous use

NDA: 211226

In response to DOP 2's consult request dated January 24, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for BRAND NAME (levoleucovorin).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP 2 (Autumn Zack-Taylor) on July 17, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 26, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at (301) 796-0575 or carole.broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
08/01/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 16, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 211226
Product Name and Strength:	Levoleucovorin for injection, 175 mg, and 300 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Spectrum Pharmaceuticals, Inc.
FDA Received Date:	December 22, 2017 and March 9, 2018
OSE RCM #:	2018-552
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of NDA 211226, this review evaluates the proposed levoleucovorin container labels, carton labeling, and prescribing information (PI) to identify areas of vulnerability that could lead to medication errors. The Division of Oncology Products 2 (DOP2) requested this review as part of their evaluation of this 505(b)(2) application seeking approval for levoleucovorin for injection submitted on December 22, 2017. The listed drugs are Fusilev (NDA 020140) and leucovorin calcium (NDA 008107).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of materials found the proposed levoleucovorin container labels, carton labeling, and PI may be improved to promote safe use of this product.

We note the strength presentation on container labels and carton labeling is expressed in milligrams of (b) (4) levoleucovorin (b) (4). We also note the March 9, 2018 PI submission expresses the strength in milligrams of levoleucovorin free acid (175 mg and 300 mg). We contacted CMC via email on April 18, 2018 regarding the correct presentation of strength on container labels, carton labeling, and PI. Subsequently, CMC sent an Information Request to the Sponsor on April 24, 2018 stating, "...the established name for the proposed drug product should be revised to Levoleucovorin for Injection as approved for the reference product; and the drug strength presented on the product labels...should be revised to reflect

the content of levoleucovorin (b) (4) [a]" Therefore, we base our recommendations for container labels, carton labeling and PI based on the fact that the strength should be presented in milligrams of levoleucovorin free acid (175 mg and 300 mg).

4 CONCLUSION & RECOMMENDATIONS

We conclude the container labels, carton labeling, and PI for levoleucovorin may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    1. Please see Appendix H for our PI recommendation in tracked changes.

4.2 RECOMMENDATIONS FOR SPECTRUM PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)
    1. Revise the established name to read "(Levoleucovorin) for Injection" and remove (b) (4)
    2. Revise the strength expression to read "175 mg/vial" and "300 mg/vial" on the principal display panel (PDP) for consistency with the proposed PI submitted on March 9, 2018 (b) (4)
    3. Revise the container labels and carton labeling to include the use of different colors, boxing, or some other means to provide adequate differentiation between the different strengths to mitigate the risk of wrong strength selection or dosing errors. As currently proposed, there is inadequate strength differentiation between the 175 mg and 300 mg strengths, (b) (4)
    4. Revise the product code in the NDC numbers to ensure the middle 3 or 4 digits are different and non-sequential between strengths. As currently presented, the (b) (4) The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation.[b]

[a] Kinsley, S. "NDA 211226 CMC Information Request on Request 4-24-18" Message to Anil Hiteshi. Silver Spring (MD): FDA, CDER, OND, DOP2 (US); 2018 APR 24.

[b] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

5. Ensure the lot number and expiration date are clearly differentiated from one another and are not located in close proximity to other numbers where the numbers can be mistaken as the lot number.[c,d]
6. Consider revising the storage and handling statement from "...excursions from 15-30° C (59-86 °F)" to "...excursion from 15 °C -30 °C (59 °F -86 °F)" to include the unit of measurement after each numerical temperature value.
7. Revise package type term from (b) (4) to "Single-dose vial-Discard Unused Portion."
8. Change the statement, "Usual Dosage: (b) (4)." to read, "Usual Dosage: See Prescribing information."
9. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you wish to use. We recommend using a format such as MMMYYY (e.g. JAN2019) or MMMDDYYY (e.g. JAN312019).
10. As proposed, mannitol is expressed as "mg/mL" on container labels and carton labeling but expressed as "mg" in PI (Section 11). Clarify which expression you intend to use across all labels and labeling (container labels, carton labeling, and PI) for consistency.

B. Container Labels
    1. We note the presence of the barcode placeholder, but please submit updated container labels with the actual linear barcode instead of the placeholder for our review.

C. Carton Labeling
    1. Decrease the prominence of statement "Rx Only" as this information appears more prominent than the established name on the principal display panel.

[c] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert A cute Care. 2014;19(23):1-4.

[d] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for levoleucovorin received on December 22, 2017 and March 9, 2018 from Spectrum Pharmaceuticals, Inc., and the listed drugs (LD).

Table 2. Relevant Product Information for levoleucovorin and the Listed Drugs

Product Name	**levoleucovorin**	**Fusilev**	**Leucovorin calcium** (NDA 008107 withdrawn, product discontinued)
Initial Approval Date	N/A	March 7, 2008	June 20, 1952
Active Ingredient	levoleucovorin	levoleucovorin calcium	leucovorin calcium
Indication	• Rescue after high-dose methotrexate therapy in osteosarcoma. • Diminish toxicity and (b) (4) effects of impaired methotrexate elimination and of (b) (4) overdosage of folic acid antagonists. • Use in combination chemotherapy with 5-flourouracil in the (b) (4) treatment of patients with (b) (4) metastatic colorectal cancer.	• Rescue after high-dose methotrexate therapy in osteosarcoma. • Diminish toxicity and counteracting the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists. • Use in combination chemotherapy with 5-flourouracil in the palliative treatment of patients with advanced metastatic colorectal cancer.	• Rescue after high-dose methotrexate therapy in osteosarcoma. • Diminish toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists. • For use in combination with 5-flourouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer. • Treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is feasible.
Route of Administration	Intravenous	Intravenous	Intravenous
Dosage Form	For injection	For injection	For injection
Strength	175 mg and 300 mg	50 mg/vial	350 mg/vial
Dose and Frequency	Rescue after high-dose methotrexate therapy and Diminish toxicity and (b) (4)	Rescue after high-dose methotrexate therapy and Diminish toxicity	Rescue at high-dose methotrexate therapy

	effects of impaired methotrexate elimination • 5 mg/m^2 intravenous infusion every 6 hours for 10 doses; or 50 mg/m^2 intravenous infusion every 3 hours Use in combination chemotherapy with 5-fluorouracil (5-FU) • 100 mg/m^2 by slow intravenously over a minimum of 3 minutes or 10 mg/m^2 followed by 5-FU at 370 mg/m2 or 425 mg/m^2, respectively.	and counteracting the effects of impaired methotrexate elimination • 5 mg/m^2 intravenous infusion every 6 hours for 10 doses; or 50 mg/m^2 intravenous infusion every 3 hours Use in combination chemotherapy with 5-fluorouracil (5-FU) • 100 mg/m^2 intravenously over a minimum of 3 minutes or 10 mg/m^2 followed by 5-FU at 370 mg/m^2 or 425 mg/m^2, respectively.	• 15 mg (approximately 10 mg/m^2 every 6 hours for 10 doses Impaired methotrexate elimination or inadvertent overdosage • 10 mg/m^2 every 6 hours until the serum methotrexate level is less than 10^{-8}M Megaloblastic anemia due to folic acid deficiency • Up to 1 mg daily Advanced colorectal cancer • 200 mg/m^2 by intravenous injection over a minimum of 3 minutes, followed by 5-FU at 370 mg/m^2 by intravenous injection • 20 mg/m^2 by intravenous injection, followed by 5-FU at 425 mg/m^2 by intravenous injection
How Supplied	Single-use vial	Single-use vial	Single-use vial
Storage	Store at (b) (4) in carton until contents are used. Excursions permitted from 15-30° C (59-86 °F). Protect from light.	Store at (b) (4) in carton until contents are used. (b) (4) Protect from light.	Store at 25° C (77 °F); excursions permitted from 15-30° C (59-86 °F). Protect from light.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following levoleucovorin labels and labeling submitted by Spectrum Pharmaceuticals, Inc.

- Container label received on December 22, 2017
- Carton labeling received on December 22, 2017
- Prescribing Information (Image not shown) received on March 9, 2018

G.2 Label and Labeling Images

Container Labels

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[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

COLLEEN L LITTLE
05/16/2018

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05/16/2018