CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212937Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	September 20, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 212937
Product Name and Strength:	Pedmark (sodium thiosulfate) Injection, 12.5 g/ 100 mL
Applicant/Sponsor Name:	Fennec Pharmaceuticals, Inc.
OSE RCM #:	2019-2395-4
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on September 1, 2022 for Pedmark. The Division of Oncology 2 (DO2) requested that we review the revised carton labeling for Pedmark (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

Since our previous label and labeling review, there were further discussions during labeling meetings and continued labeling negotiations with the Applicant related to the non-substitutability considerations for this product. Based on the exchange of information, we reached the understanding that the review team supports the inclusion of the non-substitutable statements in the PI and on the container label and carton labeling. Thus, the team decided the statements will remain as proposed.

We have no additional recommendations at this time.

[a] Stewart, J. Label and Labeling Review for Pedmark (NDA 212937). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUN 17. RCM No.: 2019-2395-3.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 1, 2022

Container label- received on March 23, 2022

(b) (4)

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JANINE A STEWART
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ASHLEIGH V LOWERY
09/20/2022 11:32:22 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 24, 2022
To:	Maritsa Stephenson, PharmD, BCPS Regulatory Health Project Manager **Division of Oncology 2 (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	PEDMARK (sodium thiosulfate injection)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	NDA 212937
Applicant:	Fennec Pharmaceuticals, Inc.

1 INTRODUCTION

On March 23, 2022, Fennec Pharmaceuticals, Inc. submitted for the Agency's review a Class 2 Resubmission of their original New Drug Application (NDA) 212937 for PEDMARK (sodium thiosulfate injection) in response to a Complete Response (CR) letter issued by FDA on November 26, 2021. The proposed indication for PEDMARK (sodium thiosulfate injection) is to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumor.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 2 (DO2) on April 20, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PEDMARK (sodium thiosfulate injection).

2 MATERIAL REVIEWED

- Draft PEDMARK (sodium thiosulfate injection) PPI received on March 23, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 15, 2022.
- Draft PEDMARK (sodium thiosulfate injection) Prescribing Information (PI) received on March 23, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 15, 2022.
- DMPP and OPDP collaborative review of PEDMARK (sodium thiosulfate injection) PPI dated July 7, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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BARBARA A FULLER
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LASHAWN M GRIFFITHS
08/24/2022 09:19:43 AM

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

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

Memorandum

Date: August 19, 2022

To: Maritsa Stephenson, PharmD, BCPS, Regulatory Project Manager
Division of Oncology 2 (DO2)

From: Emily Dvorsky, Team Leader
Office of Prescription Drug Promotion (OPDP)

CC: Lynn Panholzer, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for PEDMARK™ (sodium thiosulfate injection), for intravenous use

NDA: 212937

In response to DO2's consult request dated April 20, 2022, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the March 23, 2022 Class 2 Resubmission of the NDA for PEDMARK™ (sodium thiosulfate injection), for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO2 (Stephenson) on August 15, 2022, and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 23, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at Emily.Dvorsky@fda.hhs.gov.

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/s/

EMILY M DVORSKY
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LABEL AND LABELING REVIEW MEMORANDUM
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	June 17, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 212937
Product Name, Dosage Form, and Strength:	Pedmark (sodium thiosulfate) Injection, 12.5 g/ 100 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fennec Pharmaceuticals, Inc.
FDA Received Date:	March 23, 2022
OSE RCM #:	2019-2395-3
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the review process of this Class 2 Resubmission for Pedmark Injection, this review evaluates the proposed container label, carton labeling, Patient Information, and Prescribing Information for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

On May 27, 2021, Fennec submitted a Class 2 Resubmission response to the August 10, 2020 CR letter. The resubmission included for our review a proposed PI, a container label and carton labeling revised in accordance with USP. Our evaluation of the proposed container label, carton labeling, Prescribing Information, and Patient Information found the materials acceptable from a medication error perspective, which we documented in our review dated September 20, 2021[a].

During subsequent labeling negotiations, Fennec proposed adding the statement (b) (4) to the *Dosage and Administration* sections of the Highlights of Prescribing Information (HPI) and the Full Prescribing Information (FPI). In an effort to discourage the use of the sodium thiosulfate products that are indicated for the treatment of cyanide poisoning as a substitute for Pedmark for otoprotection, the Agency revised the proposed statement to read "PEDMARK is not substitutable with other sodium thiosulfate products". Based on this statement being added to the PI, Fennec proposed an updated Pedmark container label and carton labeling, PI and Patient Information which included a similar statement regarding the non-substitutability of Pedmark with other marketed sodium thiosulfate products in submissions dated October 14, 2021 and October 15, 2021. Subsequently, the Agency issued a Complete Response to NDA 212937 on November 26, 2021 for inspection and manufacturing processes and clinical concerns related to hypophosphatemia and hyponatremia. On March 23, 2022, Fennec re-submitted the label and labeling components in a Class 2 Resubmission response to the November 26, 20201 CR Letter.

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 Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A

[a] Stewart J. Label and Labeling Review Memorandum for Pedmark (NDA 212937). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEP 20. RCM No.: 2019-2395-2.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
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 or ISMP Newsletters 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

We performed a risk assessment of the proposed container label, carton labeling, Prescribing Information, and Patient Information. Of concern is the statement "Do Not Substitute with Other Sodium Thiosulfate Products", which is proposed on the revised container label and carton labeling and the statement "PEDMARK is not substitutable with other sodium thiosulfate products" appears in the Dosage and Administration section HPI and in the FPI.

For products with a new formulation that is not substitutable with a currently marketed formulation, statements regarding non-substitutability which appear in the Dosage and Administration sections of the HPI and the FPI should include the reason for non-substitutability. For example:

- HPI: To avoid substitution errors and overdosage, do not substitute for other [active ingredient] products on a milligram-per-milligram basis because [*provide reason*].
- FPI: Do not substitute [TRADENAME] for other sodium thiosulfate products on a milligram-per-milligram basis even if the total milligram strength is the same, because [*provide reason here*]. *[see Clinical Pharmacology (12.3)].*

Based on this information, we met with members of the review team to understand the rationale and the safety concern that the non-substitutability statements were intended to address.

We understand the intent of the proposed statements is to discourage the use of the sodium thiosulfate products that are indicated for the treatment of cyanide poisoning as a substitute for Pedmark for otoprotection. However, there is no identified safety or efficacy concern if these products are used interchangeably at the correct dosage and no data to support adding non-substitutability statements to the PI.

Further, the goal of labeling is to ensure that a product is used safely and effectively according to its approved indication. Therefore, rather than labeling a product with information regarding what not to use for the indication, we endeavor to optimize the product's labeling to clearly express the information that will support its safe and effective use. We note the example of Hope Pharmaceutical's Sodium Thiosulfate Injection, USP (NDA 203923). The

carton labeling for this product explicitly states the product's indication and provides dosage and administration information that is available to the user at the point of use.

Thus, we provide related recommendations below in Section 4.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Pedmark PI, container label, and carton labeling can be improved to promote the safe use of the product. We provide recommendations for DO2 in Section 4.1 and recommendations for Fennec Pharmaceuticals, Inc. in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section (HPI and FPI)

a. We recommend deleting the statement "PEDMARK is not substitutable with other sodium thiosulfate products" which appears in the Dosage and Administration section HPI and in the FPI. Upon further review team evaluation, this statement is not necessary since the differences between Pedmark and other sodium thiosulfate products are stated in their respective PIs (e.g., Indication, Dosage & Administration, How Supplied, etc.).

4.2 RECOMMENDATIONS FOR FENNEC PHARMACEUTICALS, INC.

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

A. General Comments (Container labels & Carton Labeling)

1. For products with a new formulation that is not substitutable with a currently marketed formulation, statements regarding non-substitutability which appear in the Dosage and Administration sections of the HPI and the FPI should include the reason for non-substitutability. For example:
    - HPI: To avoid substitution errors and overdosage, do not substitute for other [active ingredient] products on a milligram-per-milligram basis because [*provide reason*].
    - FPI: Do not substitute [TRADENAME] for other sodium thiosulfate products on a milligram-per-milligram basis even if the total milligram strength is the same, because [*provide reason here*]. *[see Clinical Pharmacology (12.3)].*

    Remove the statement that reads "Do Not Substitute with Other Sodium Thiosulfate Products". A difference in indication does not support adding a non-substitutability statement to the container label and carton labeling. We recommend instead stating the indication as described in B.1 below.

B. Carton Labeling

1. To ensure that Pedmark is used safely and effectively according to its proposed indication, we recommend adding the indication to appear on the Pedmark carton labeling. To achieve this aim, we recommend the following revisions to the carton labeling:

    a. Relocate the "Distributed By: ", the website address, and the trademark statement to appear on the opposite side panel below the storage information.

2. On the side panel where space permits, add the dosage and administration information to read similar to the following example:

Dosage and Administration*

Actual Body Weight	To reduce the risk of ototoxicity associated with cisplatin in patients 1 month or older
Less than 5 kg	10 g/m^2
5 to 10 kg	15 g/m^2
Greater than 10 kg	20 g/m^2

    a. Include a statement under Dosage and Administration table to alert the healthcare provider that additional important information is in the FPI. (e.g., *See Full Prescribing Information for instructions on preparation and administration of this product.)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pedmark received on March 23, 2022 from Fennec Pharmaceuticals, Inc..

	Pedmark	Sodium Thiosulfate (Hope Pharmaceuticals)
Application #	NDA 212937 (pending)	NDA 203923 (approved)
Indication	PEDMARK is indicated to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.	Sodium Thiosulfate Injection is indicated for sequential use with sodium nitrite for the treatment of acute cyanide poisoning that is judged to be serious or life-threatening. When the diagnosis of cyanide poisoning is uncertain, the potential risks associated with Sodium Thiosulfate Injection should be carefully weighed against the potential benefits, especially if the patient is not in extremis.
Route	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	12.5 gm/100 ml (125 mg/ml)	12.5 g/50 mL (250 mg/mL)
Dose and Frequency	infants less than 5 kg: 10g/m^2 infants & children 5 -10 kg: 15 g/m^2 patients > 10 kg: 20 g/m^2 (based on actual body weight) Administer PEDMARK as an intravenous infusion over 15 minutes, following cisplatin infusions that are 1 to 6 hours in duration.	Age: Intravenous Dose of Sodium Nitrite and Sodium Thiosulfate Adults: 1.) Sodium Nitrite – 10 mL of sodium nitrite at the rate of 2.5 to 5 mL/minute 2.) Sodium Thiosulfate – 50 mL of sodium thiosulfate immediately following administration of sodium nitrite. Children: 1.) Sodium Nitrite – 0.2 mL/kg (6 mg/kg or 6-8 mL/m^2 BSA) of sodium nitrite at the rate of 2.5 to 5 mL/minute not to exceed 10 mL 2.) Sodium Thiosulfate – 1 mL/kg of body weight (250 mg/kg or approximately 30-40 mL/m^2 of BSA) not to exceed

			50 mL total dose (10 g) immediately following administration of sodium nitrite.
How Supplied	Carton containing one 100 mL glass vial of sodium thiosulfate injection	Carton containing one 50 mL glass vial of sodium thiosulfate injection	
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).	Store at controlled room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted from 15 to 30°C (59 to 86°F). Protect from direct light. Do not freeze.	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 12, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Pedmark. Our search identified 3 previous reviews[b,c,d], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Stewart J. Label and Labeling Review Memorandum for Pedmark (NDA 212937). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEP 20. RCM No.: 2019-2395-2.

[c] Stewart J. Label and Labeling Review Memorandum for Pedmark (NDA 212937). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 29. RCM No.: 2019-2395-1.

[d] Stewart J. Label and Labeling Review for Pedmark (NDA 212937). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 14. RCM No.: 2019-2395.

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 Pedmark labels and labeling submitted by Fennec Pharmaceuticals, Inc..

- Container label received on March 23, 2022
- Carton labeling received on March 23, 2022
- Patient Information (Image not shown) received on March 23, 2022 available from: \\CDSESUB1\evsprod\nda212937\0029\m1\us\patient-information-clean.doc
- Prescribing Information (Image not shown) received on March 23, 2022 available from: \\CDSESUB1\evsprod\nda212937\0021\m1\us\draft-labeling-text-clean.docx

G.2 Label and Labeling Images

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 13, 2021
To:	Idara Ojofeitimi, MS Chief, Project Management Staff **Division of Oncology 2 (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	PEDMARK (sodium thiosulfate injection)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	NDA 212937
Applicant:	Fennec Pharmaceuticals, Inc.

1 INTRODUCTION

On May 27, 2021, Fennec Pharmaceuticals, Inc. submitted for the Agency's review a Class 2 Resubmission of their original New Drug Application (NDA) 212937 for PEDMARK (sodium thiosulfate injection) in response to a Complete Response (CR) letter issued by FDA on August 10, 2020. The proposed indication for PEDMARK (sodium thiosulfate injection) is to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumor.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 2 (DO2) on September 24, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PEDMARK (sodium thiosfulate injection).

2 MATERIAL REVIEWED

- Draft PEDMARK (sodium thiosulfate injection) PPI received on May 27, 2021, and received by DMPP and OPDP on October 5, 2021.
- Draft PEDMARK (sodium thiosulfate injection) Prescribing Information (PI) received on May 27, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 5, 2021.
- DMPP and OPDP collaborative review of PEDMARK (sodium thiosulfate injection) PPI dated July 7, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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

Memorandum

Date: October 8, 2021

To: Idara Ojofeitimi, Regulatory Project Manager, Division of Oncology 2 (DO2)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for PEDMARK™ (sodium thiosulfate injection), for intravenous use

NDA: 212937

In response to DO2's consult request dated September 24, 2021, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the May 27, 2021 Class 2 Resubmission of the NDA for PEDMARK™ (sodium thiosulfate injection), for intravenous use.

OPDP reviewed the proposed PI received by electronic mail from DO2 on October 5, 2021, and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the proposed PPI will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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LYNN M PANHOLZER
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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:	July 29, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 212937
Product Name and Strength:	Pedmark (sodium thiosulfate) Injection (b) (4)
Applicant/Sponsor Name:	Fennec Pharmaceuticals, Inc.
OSE RCM #:	2019-2395-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 27, 2020 for Pedmark. Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Pedmark (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 Applicant implemented all of our recommendations for the Pedmark container label and we have no additional recommendations for the Pedmark container label at this time.

However, we note the revised carton labeling contains a boxed statement that reads, (b) (4) The proposed Pedmark carton labeling can be improved to promote the safe and effective use of this product.

3 RECOMMENDATIONS FOR FENNEC PHARMACEUTICALS, INC.

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

A. Carton Labeling

[a] Stewart J. Label and Labeling Review for Pedmark (NDA 212937). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 14. RCM No.: 2019-2395.

a. As proposed, the carton labeling submitted to this marketing application indicates the product is [redacted] (b) (4) Remove the boxed statement that reads [redacted] (b) (4)

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 27, 2020

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 7, 2020
To:	Anuja Patel, MPH Lead Regulatory Project Manager **Division of Oncology 2 (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	PEDMARK (sodium thiosulfate injection)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	NDA 212937
Applicant:	Fennec Pharmaceuticals, Inc.

1 INTRODUCTION

On February 10, 2020, Fennec Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 212937 for PEDMARK (sodium thiosulfate injection). The proposed indication is for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 2 (DO2) on May 7, 2020 and April 10, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PEDMARK (sodium thiosulfate injection).

2 MATERIAL REVIEWED

- Draft PEDMARK (sodium thiosulfate injection) PPI received on February 10, 2020, and received by DMPP and OPDP on June 29, 2020 and June 26, 2020, respectively.
- Draft PEDMARK (sodium thiosulfate injection) Prescribing Information (PI) received on February 10, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 29, 2020 and June 26, 2020, respectively.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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

Memorandum

Date: July 7, 2020

To: Anuja Patel, Lead Regulatory Project Manager
Division of Oncology 2 (DO2)

Stacy Shord, PharmD, Associate Director for Labeling, DO2

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for PEDMARK™ (sodium thiosulfate injection), for intravenous use

NDA: 212937

In response to DO2's consult request dated April 10, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for PEDMARK™ (sodium thiosulfate injection), for intravenous use.

PI and PPI: OPDP's comments on the proposed PI are based on the draft PI received by electronic mail from DO2 on June 26, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the PPI, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Applicant to the electronic document room on February 10, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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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:	June 14, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 212937
Product Name, Dosage Form, and Strength:	Pedmark (b) (4) Injection, (b) (4)
Total Product Strength:	(b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fennec Pharmaceuticals, Inc.
FDA Received Date:	February 10, 2020 and April 15, 2020
OSE RCM #:	2019-2395
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the review process for this NDA, this review evaluates the proposed Pedmark Prescribing Information (PI), Patient Package Insert (PPI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

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 Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
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 or ISMP Newsletters 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 that the proposed Pedmark PI, container label, and carton labeling may be improved to promote safe use of this product. Thus, we provide related recommendations below in Section 4.

We note the use of the term (b) (4) in the labels and labeling and we communicated this to OPQ. We defer to OPQ to determine the appropriate package type term for this product.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Pedmark PI and container label can be improved to increase the clarity, and to promote the safe use of the product. We provide recommendations for DO2 in Section 4.1 and recommendations for Fennec Pharmaceuticals, Inc. in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Highlights and Full Prescribing Information

1. Dosage and Administration Section

a. Revise the statement [redacted] to read [redacted] to avoid the risk of end users inadvertently overlook the [redacted] in the statement, thus preventing the risk of wrongly reading the statement [redacted]

c. Consider replacing the symbols “>” and “<” with their intended meaning to prevent misinterpretation and confusion.

d. As proposed, the dosing table lists the dose in order of the highest weight to the lowest weight. Consider revising the table to present the dosing information in ascending order starting with the lowest weight (less than 5 kg) to the highest weight (greater than 10 kg) to support the safe use of the product.

e. As proposed, the dosing table contains [redacted] This information is not necessary and may cause confusion as to if the gram weight or the milliliter volume should be used in calculating a BSA-based dose, which may lead to medication errors. We anticipate the weight (g) will be used for the BSA-based dose calculation for this proposed product in the usual practice setting, thus we recommend removing [redacted] to mitigate the risk of confusion and to promote the safe use of the product.

2. How Supplied/Storage and Handling Section

a. Consider revising the presentation of information in Section 16: How Supplied/Storage and Handling to improve readability; for example, as follows:

How Supplied

Pedmark [redacted] injection is a clear, colorless, sterile solution [redacted] single-dose vial supplied as:

[redacted]

[redacted]

B. Patient Package Insert (PPI)

1. Under "What is PEDMARK?",
   a. Revise the statement [redacted] to read [redacted] to improve clarity and for verbiage consistency within the PPI. Consider relocating this statement to [redacted]
   b. Revise the statements [redacted] as this infusion information is already provided under [redacted].
2. Revise the bullet [redacted] to read [redacted] for verbiage consistency. See recommendation B.1.a, consider merging the statements with this bullet.
3. Under [redacted], consider replacing the words [redacted] with [redacted] in the statement [redacted].

4.2 RECOMMENDATIONS FOR FENNEC PHARMACEUTICALS, INC.

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

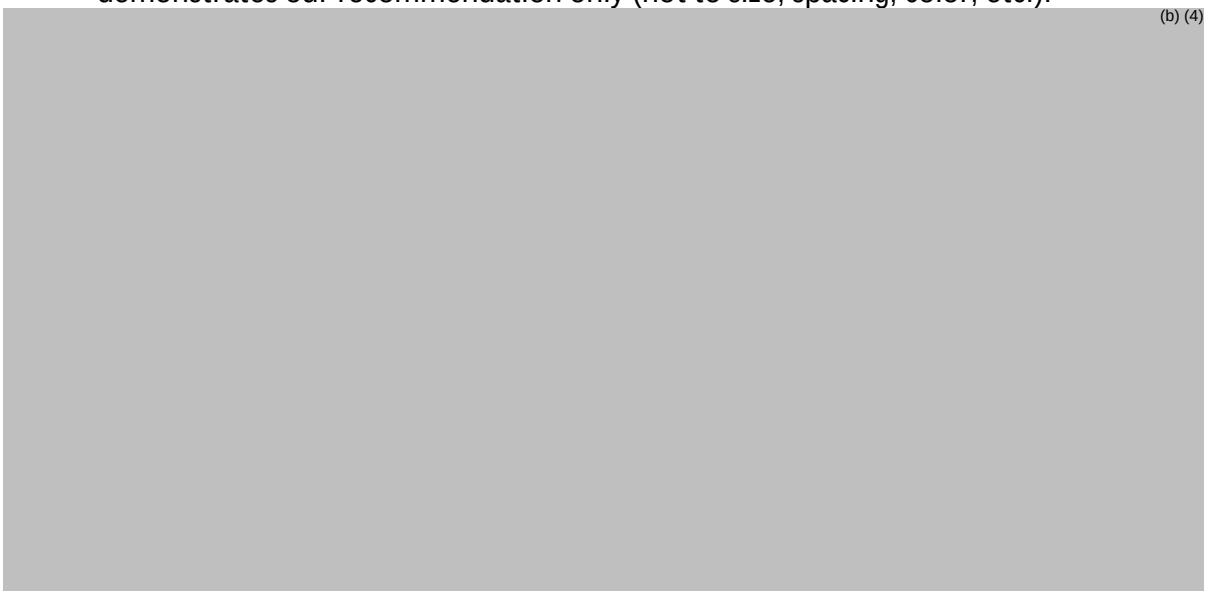
A. General Comments (Container label & Carton Labeling)

1. 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 intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. To ensure consistency with the Prescribing information, revise the statement (b) (4) to read "Recommended Dosage: See prescribing information."

B. Container Label

1. To improve readability, place adequate space between the numerical dose and unit of measure (b) (4)
2. Revise the statement (b) (4) to read "100 mL" as the appropriate package-type term "Single-dose vial" already appears on the container label.
3. Revise the container label so important product information critical for the use of the proposed drug product, is prominently displayed on the Principal Display Panel (PDP), similar to the layout on the proposed carton labeling. This may be achieved by relocating other information to a side panel. Example layout below demonstrates our recommendation only (not to size, spacing, color, etc.).



C. Carton Labeling

1. As proposed, important product information on the front, top, and side panels of the carton labeling appear in small font size that may be difficult for users to read. Increase the font size of the net quantity statement, NDC number, package type term, recommended dosage, storage information, manufacturer information, and Lot/Exp/Sn to improve the readability of the information.
2. Revise the net quantity statement (b) (4) to read "100 mL" as the appropriate package-type term "Single-dose vial" already appears on the front and back panels.

3. Delete the small font size statement [redacted] (b) (4) on the front panel because this is already presented on the front panel in larger font size after the "Single-Dose Vial" statement.
4. Consider relocating the statement "Recommended Dosage: See prescribing information." from the front panel to the side panel (see recommendation A.2).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pedmark received on February 10, 2020 from Fennec Pharmaceuticals, Inc..

Table 2. Relevant Product Information for Pedmark	
Initial Approval Date	N/A
Active Ingredient	sodium thiosulfate (b) (4)
Indication	For the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors.
Route of Administration	Intravenous Infusion
Dosage Form	Injection
Strength	(b) (4)
Dose and Frequency	(b) (4)
How Supplied	Supplied as 100 mL of a clear, colorless, sterile solution in flint glass vials with rubber stoppers and capped with aluminum over-seals.
Storage	(b) (4) between 15°C and 30°C (59°F and 86°F)
Container Closure	100 mL (b) (4) clear glass vial with a 32 mm (b) (4) rubber stopper and a aluminum seal with green matte top plastic button

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 14, 2020, we searched for previous DMEPA reviews relevant to this current review using the term, sodium thiosulfate. Our search identified 2 previous reviews[a,b], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Wilson, V. Label and Labeling Review for Sodium Thiosulfate (NDA 203922 (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 30. RCM No.: 2018-1331.

[b] Baugh, D. Label and Labeling Review for Sodium Thiosulfate (NDA 203922). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 JAN 23. RCM No.: 2012-117.

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,[c] along with postmarket medication error data, we reviewed the following Pedmark labels and labeling submitted by Fennec Pharmaceuticals, Inc..

- Container label received on February 10, 2020
- Carton labeling received on February 10, 2020
- Prescribing Information (Image not shown) received on February 10, 2020, available from \\cdsesub1\evsprod\nda212937\0002\m1\us\11413-draft-labeling-text.docx
- Patient Package Insert (Image not shown) received on April 15, 2020, available from \\cdsesub1\evsprod\nda212937\0009\m1\us\patient-information.pdf

G.2 Label and Labeling Images

Container label

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

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