CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216686Orig1s000

<u>OTHER REVIEW(S)</u>

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TO: NDA 216686

FROM: Meshaun Payne, Senior Regulatory Project Manager
Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

SUBJECT: Division of Gastroenterology (DG) pediatric consult request to the Division of Pediatric and Maternal Health (DPMH) requesting Labeling Review and PeRC Preparation Assistance

DRUG: FOCINEV (Fosaprepitant injection)

DG submitted a consult request to DPMH on January 31, 2022, asking for pediatric and maternal health input regarding the sponsor's labeling for the above 505(b)(2) NDA product, indicated for acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer therapy (HEC) including high-dose cisplatin; delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

DPMH was also requested to assist in drafting the proposed PREA PMR for this product and to attend the upcoming PeRC Meeting.

DPMH submitted a consult to Office of the Chief Counsel (OCC) on August 3, 2022 requesting their input on the labeling for this 505(b)(2) NDA product. DPMH and OCC attended the Division's Internal meeting held on May 12, 2022, and wrap-up meeting held on September 14, 2022. DPMH also attended the PeRC Meeting held on September 20, 2022. DPMH and OCC comments and recommendations are incorporated within the final labeling. See the following key documents in DARRTS:

- Pediatric Template
- September 20, 2022, PeRC Meeting Minutes
- Final labeling
- Complete Response Letter dated October 19, 2022

The Sponsor's resubmission was received by the Agency on February 28, 2023. The resubmission was to address the deficiencies identified in the Complete Response Letter dated October 19, 2022. Subsequently the consult to DPMH was re-opened on March 2, 2023.

DPMH attended the Division's internal meetings held on March 17, 2023, May 31, 2023, June 14, 2023, and July 11, 2023.

DPMH has no further comments regarding this consult. This memorandum will close out the consult request.

DPMH Pediatric Reviewer – Sonaly McClymont
DPMH Pediatric Team Leader – Shetarra Walker
DPMH Maternal Health Reviewer – Christos Mastroyannis
DPMH Maternal Health Team Leader – Tamara Johnson
OCC Representative – Nancy Boocker
RPM for DPMH – Meshaun Payne
Lead Consumer Safety Officer for DPMH – Rosemary Addy

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/s/

MESHAUN L PAYNE
08/07/2023 03:28:44 PM

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

PATIENT LABELING REVIEW

Date:	July 20, 2023
To:	Mary Chung Regulatory Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	FOCINVEZ (fosaprepitant)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	NDA 216686
Applicant:	Spes Pharmaceuticals Inc.

1 INTRODUCTION

On February 28, 2023, Spes Pharmaceuticals Inc. submitted for the Agency's review a Resubmission-Complete Response to Deficiencies in Complete Response Letter (CRL) to the Original New Drug Application (NDA) Submission under 505(b)(2) Regulatory Pathway for FOCINVEZ (fosaprepitant) injection, for intravenous use.

The proposed indication for FOCINVEZ (fosaprepitant) injection, for intravenous use is for use in adults and pediatric patients 6 months of age and older, in combination with other antiemetic agents, for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

FOCINVEZ has not been studied for treatment of established nausea and vomiting.

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 Gastroenterology (DG) on March 28, 2023, and March 27, 2023, respectively for DMPP and OPDP, to review the Applicant's proposed Patient Package Insert (PPI) for FOCINVEZ (fosaprepitant) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft FOCINVEZ (fosaprepitant) injection, for intravenous use PPI received on February 28, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 11, 2023.
- Draft FOCINVEZ (fosaprepitant) injection, for intravenous use Prescribing Information (PI) received on February 28, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 11, 2023.
- EMEND (fosaprepitant) for injection, for intravenous use comparator labeling dated May 2, 2022.

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 have:

- 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 20, 2023

To: Mary Chung, Project Manager, DG

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for FOCINVEZ (fosaprepitant injection) for intravenous use

NDA: 216686

In response to DG's consult request dated March 27, 2023, OPDP has reviewed the proposed product labeling (PI), and patient labeling (PPI) for Focinvez.

OPDP has no comments on the PI.

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.

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 5, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 216686
Product Name, Dosage Form, and Strength:	Focinvez (fosaprepitant injection), 150 mg/50 mL (3 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	SPES Pharmaceuticals
FDA Received Date:	February 28, 2023
TTT ID #:	2023-3908
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Focinvez (fosaprepitant injection), the Division of Gastroenterology (DG) requested that we review the proposed Focinvez prescribing information, carton labeling, and vial hanger label for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

SPES previously submitted NDA 216686 on December 23, 2021. The application received a complete response (CR) on October 19, 2022. Thus, SPES submitted a response to the CR on February 28, 2023. DMEPA previously reviewed the proposed labels and labeling (see Appendix B). The Applicant resubmitted their NDA with a revised container label and carton labeling addressing recommendations we made during a previous review.

3 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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

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

4 CONCLUSION & RECOMMENDATIONS

We previously reviewed the proposed prescribing information, container label, and carton labeling. The Applicant implemented all of our recommendations and they are acceptable from a medication error perspective. We have no additional recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Focinvez received on February 28, 2023 from SPES Pharmaceuticals, and the listed drug (LD).

Table 2. Relevant Product Information for Focinvez and the Listed Drug		
Product Name	Focinvez	Emend[a]
Initial Approval Date	N/A	January 25, 2008
Active Ingredient	fosaprepitant injection	
Indication	in adults and pediatric patients 6 months of age and older, in combination with other antiemetic agents, for the prevention of: •acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. •delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)	
Route of Administration	Intravenous infusion	
Dosage Form	injection	For injection
Strength	150 mg/50 mL (3 mg/mL)	150 mg per vial
Dose and Frequency	Adults: 150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes Single Dose Regimen for the Prevention of Nausea and Vomiting Associated with Single-Day Regimens of HEC or MEC in Pediatric Patients 6 Months to 17 Years: • 12 Years to 17 Years: 150 mg intravenously over 30 minutes • 2 Years to less than 12 Years: 4 mg/kg (maximum dose 150 mg) intravenously over 60 minutes • 6 Months to less than 2 Years: 5 mg/kg (Maximum Dose 150 mg) intravenously Over 60 Minutes 3-Day Dosage Regimen for Prevention of Nausea and Vomiting Associated with Single or Multi-day Regimens of HEC or MEC in Pediatric Patients 6 Months to 17 Years: • 12 Years To 17 Years: 115 mg intravenously over 30 minutes	

[a] Emend [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2023 MAR 23. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022023s021lbl.pdf.

	• 6 Months to less than 12 Years: 3 mg/kg (maximum dose 115 mg) intravenously over 60 minutes	
How Supplied	1 vial per carton	1 vial per carton
Storage	Refrigerate FOCINVEZ at 2°C to 8°C (36°F to 46°F). FOCINVEZ vials, when kept in original carton, can remain at room temperature 20°C to 25°C (68°F to 77°F) for up to 90 days.	Emend for injection vials must be refrigerated, store at 2°C-8°C (36°F-46°F). The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 23, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, “Focinvez”. Our search identified three previous reviews, and we confirmed that our previous recommendations were implemented.

Abraham, S. Label and Labeling Review for Focinvez (NDA 216686). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 10. OSE RCM No.: 2021-2471.

Abraham, S. Label and Labeling Review for Focinvez (NDA 216686). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 SEP 20. OSE RCM No.: 2021-2471-1.

Abraham, S. Label and Labeling Review for Focinvez (NDA 216686). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 04. OSE RCM No.: 2021-2471-2.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

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

- Container label received on February 28, 2023
- Carton labeling received on February 28, 2023
- Prescribing Information (Image not shown) received on February 28, 2023, available from \\CDSESUB1\evsprod\NDA216686\0015\m1\us\114-labeling\draft\labeling

F.2 Label and Labeling Images

Vial Hanger Label

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

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/s/

SARAH K VEE
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TO: NDA 216686

FROM: Meshaun Payne, Senior Regulatory Project Manager
Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

SUBJECT: Division of Gastroenterology (DG) pediatric consult request to the Division of Pediatric and Maternal Health (DPMH) requesting Labeling Review and PeRC Preparation Assistance

DRUG: FOCINEV (Fosaprepitant injection)

DG submitted a consult request to DPMH on January 31, 2022, asking for pediatric and maternal health input regarding the sponsor’s labeling for the above 505(b)(2) NDA product, indicated for acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer therapy (HEC) including high-dose cisplatin; delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

DPMH was also requested to assist in drafting the proposed PREA PMR for this product and to attend the upcoming PeRC Meeting.

DPMH submitted a consult to Office of the Chief Counsel (OCC) on August 3, 2022 requesting their input on the labeling for this 505(b)(2) NDA product. DPMH and OCC attended the Division’s Internal meeting held on May 12, 2022, and wrap-up meeting held on September 14, 2022. DPMH also attended the PeRC Meeting held on September 20, 2022. DPMH and OCC comments and recommendations are incorporated within the final labeling. See the following key documents in DARRTS:

- Pediatric Template
- September 20, 2022, PeRC Meeting Minutes
- Final labeling

DPMH has no further comments. This memorandum will close out the consult request.

DPMH Pediatric Reviewer – Sonaly McClymont

DPMH Pediatric Team Leader – Shetarra Walker
DPMH Maternal Health Reviewer – Christos Mastroyannis
DPMH Maternal Health Team Leader – Tamara Johnson
OCC Representative – Nancy Boocker
RPM for DPMH – Meshaun Payne
Lead Consumer Safety Officer for DPMH – Rosemary Addy

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/s/

MESHAUN L PAYNE
10/19/2022 10:44:13 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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 4, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 216686
Product Name and Strength:	Focinvez (fosaprepitant) injection, 150 mg/50 mL (3 mg/mL)
Applicant/Sponsor Name:	Spes Pharmaceuticals Inc.
OSE RCM #:	2021-2471-2
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

On September 20, 2022, we completed a label and labeling review memo, the Applicant had implemented all of our recommendations at that time.[a] Given the recent updates to the Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, we have additional recommendations for the Applicant's consideration to be included as part of the upcoming complete response (CR) letter.

2 CONCLUSION

The revised container label is unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 3 for the Applicant.

[a]Abraham, A. Label and Labeling Review for Focinvez (NDA 216686). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 SEP 20 RCM No.: 2021-2471-1.

3 RECOMMENDATIONS FOR SPES PHARMACEUTICALS INC.

Table 1. Identified Issues and Recommendations for Spes Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	We note that you are planning to use a hanger strap to administer the product, but it is unclear if the hanger label is transparent.	The hanger attached to the infusion container should not interference with the ability to read the drug product information on the label. Additionally, the hanger should be transparent and a separate component of the label; as opposed to a portion of the drug label itself.[b]	Ensure that the hanger attached to the infusion container does not interfere with the readability of the drug product information on the label, is transparent in nature and is separate from the label itself.
2.	Container label is missing graduation marks on the side of the label.	Having graduation marks on the infusion container can help health care practitioners identify the amount of drug that remains in the infusion container during administration.[b]	Consider adding graduation marks in milliliters to the infusion container. The graduation marks should be readable when the infusion container is hung upside down for administration.

[b]Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

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/s/

SHERLY ABRAHAM
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IDALIA E RYCHLIK
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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 Gastroenterology (DG)
Application Type and Number:	NDA 216686
Product Name and Strength:	Focinvez (fosaprepitant) injection, 150 mg/50 mL (3 mg/mL)
Applicant/Sponsor Name:	Spes Pharmaceuticals Inc.
OSE RCM #:	2021-2471-1
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 12, 2022 for Focinvez. The Division of Gastroenterology (DG) requested that we review the revised container label and carton labeling for Focinvez (Appendix A) to determine if they are 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 and we have no additional recommendations at this time.

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[a]Abraham, A. Label and Labeling Review for Focinvez (NDA 216686). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 10. RCM No.: 2021-2471.

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/s/

SHERLY ABRAHAM
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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 Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	August 18, 2022
To:	Maureen Dewey, MPH, RAC Senior Regulatory Health Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	FOCINVEZ (fosaprepitant)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	NDA 216686
Applicant:	Spes Pharmaceuticals Inc.

1 INTRODUCTION

On December 10, 2021, Spes Pharmaceuticals Inc. submitted for the Agency's review an Original New Drug Application (NDA) Submission under 505(b)(2) Regulatory Pathway for FOCINVEZ (fosaprepitant) injection, for intravenous use. The proposed indication for FOCINVEZ (fosaprepitant) injection, for intravenous use is for use in adults and pediatric patients 6 months of age and older, in combination with other antiemetic agents, for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

FOCINVEZ has not been studied for treatment of established nausea and vomiting.

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 Gastroenterology (DG) on January 31, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for FOCINVEZ (fosaprepitant) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft FOCINVEZ (fosaprepitant) injection, for intravenous use PPI received on December 10, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 16, 2022.
- Draft FOCINVEZ (fosaprepitant) injection, for intravenous use Prescribing Information (PI) received on December 10, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 16, 2022.
- EMEND (fosaprepitant) for injection, for intravenous use comparator labeling dated May 2, 2022.

3 REVIEW METHODS

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

- 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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LASHAWN M GRIFFITHS
08/19/2022 10:53:49 AM

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

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

Memorandum

Date: August 18, 2022

To: Maureen Dewey, Project Manager, (DG)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for Focinvez (fosaprepitant), for intravenous use

NDA: 216686

In response to DG's consult request dated January 31, 2022, OPDP has reviewed the proposed product labeling (PI) for Focinvez.

OPDP has no comments on the proposed labeling is based on the draft labeling sent via electronic mail on August 15, 2022.

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.

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
08/18/2022 08:16:28 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	August 10, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 216686
Product Name and Strength:	Focinvez (fosaprepitant) injection, 150 mg/50 mL (3 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Spes Pharmaceuticals Inc.
FDA Received Date:	March 28, 2022
OSE RCM #:	2021-2471
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for Focinvez (fosaprepitant) injection, the Division of Gastroenterology (DG) requested that we review the proposed Focinvez prescribing information (PI), Patient Information (PPI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS 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
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
FDA Information Request and Response from Spes Pharmaceuticals	E
Labels and Labeling	F

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

Spes Pharmaceuticals, Inc submitted a 505(b)2 for Focinvez injection to reference listed drug (RLD) Emend for injection. Both the RLD and the proposed product contain the same active ingredients, identical indications, same total amount of drug (150 mg), dosing regimen, and route of administration. However, the products differ in dosage form [powder for injection (Emend for injection) vs. ready-to-use injection (Focinvez injection)], the presentation of total volume of strength (150 mg/vial for Emend for injection vs. 150 mg/50 mL Focinvez injection) and concentrations. When reconstituted and diluted, Emend for Injection has a concentration of 1 mg/mL (150 mg/150 mL) vs. the proposed Focinvez injection has a concentration of 3 mg/mL (150 mg/50 mL). The proposed Focinvez product will be supplied as *ready-to-use injection* compared to the powder for injection RLD that needs to be reconstituted and diluted. Thus, the ready-to-use injection and higher concentration may offer an additional option for healthcare providers when considering treatment with fosaprepitant injection.

From a medication error perspective, the introduction of a new dosage form and new concentration may result in wrong drug selection errors if the labeling is not sufficiently mitigated to indicate the differences in drug concentration, total volume and dosage form. We issued an information request (IR) to the Applicant on January 24, 2022, inquiring of the potential clinical consequences of drug preparation errors and resultant overdose and/or underdose of patients. On February 1, 2022, the Applicant responded to our IR by revising their label and labeling to address our medication error concerns. (See Appendix E). The Applicant also stated that there are no clinical, safety, and efficacy impacts of a possible 3-fold overdose and/or underdose of Focinvez in pediatric and adult populations. The DG clinical reviewer also agreed with the Applicant's rationale and conclusion. Additionally, per DG's request, Division of Pharmacovigilance (DPV-I) conducted a post-marketing safety review and agreed with Applicant's conclusion.

One of the risk mitigation strategies proposed by the Applicant is to use bold font throughout the Dosage and Administration (D&A) section of the PI to highlight the strength of Focinvez in the ready-to-use formulation of the product. However, given that there are no clinical, safety, and efficacy impacts of a possible 3-fold overdose and/or underdose of Focinvez in pediatric and adult populations, we don't recommend bolded font in the D&A section of the PI. However, we request DG to consider highlighting the concentration statement and ready-to-use statement by italicizing or underlining.

We reviewed the proposed label and labeling for Focinvez to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. The proposed PI, PPI, container label, and carton labeling may be improved to promote the safe use of the product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 for the Division and in Section 6 for Spes Pharmaceuticals.

4 CONCLUSION AND RECOMMENDATIONS

The proposed PI, PPI, container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 for the Division and in Section 6 for Spes Pharmaceuticals Inc.

5 RECOMMEDATIONS FOR DIVISION OF GASTROENTEROLOGY (DG)

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The sponsor has bolded the concentration presentation (3 mg/mL)	Per the Applicant's response dated February 1, 2022 to our January 24,	Consider highlighting the concentration statement and ready-to-use statement in

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	and ready-to-use statement.	2022 IR, they proposed to bold the new concentration and ready-to-use statement to prevent overdose and/or underdose errors.	Section 2 Dosage and Administration by italicizing or underlining.
Prescribing Information-Highlights of Prescribing Information			
1.	As currently presented, adult and pediatric dosage information and infusion time are presented together.	Lack of readability of important adult and pediatric dosing information and infusion time may lead to confusion and dosing errors.	Revise the adult and pediatric dosage information and infusion times similar to the RLD, Emend for Injection.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The statement, "Each 50 mL glass vial contains 150 mg fosaprepitant in 50 mL solution (3 mg/mL), as supplied." is found under section 2.3 Preparation of Focinvez.	The statement belongs in Section 16 How Supplied/ Storage and Handling.	Relocate the statement to Section 16 How Supplied/Storage and Handling.
2.	The statement, "FOCINVEZ is a clear, colorless solution." is found under section 2.3 Preparation of Focinvez.	Appropriate description of product characteristics important to facilitate identification of the product dosage including color description belong in Sections 3 and 16.	Delete the sentence, "FOCINVEZ is a clear, colorless solution." from Section 2.3.
3.	The negative statement, (b) (4) [redacted] is found in Section 2.3 Preparation of Focinvez.	The PI clearly states that the injection is ready-to-use. (b) (4) [redacted].	Remove the statement, (b) (4) [redacted] from the PI. (b) (4) [redacted]

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Post-marketing reports have indicated that negative statements may have the opposite effect of the intended meaning because the word ‘not’ can be overlooked and the warning be misinterpreted as an affirmative action.[a]	(b) (4) [redacted] recommend deletion of this statement.
4.	The sentences below the calculation steps including in-use storage subsection in Section 2.3 lack readability.	Lack of readability of important dosage information and storage information may cause confusion to the reader.	Consider bulleting the statements below the calculation steps in Section 2.3.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the strength presentation in total amount of drug per total volume followed by concentration statement is absent.	Ensuring the product strength is expressed as total quantity per total volume followed by the concentration per milliliter (mL) mitigates the potential for medication dosing errors.	Revise the strength presentation to express total quantity per total volume followed by the concentration statement similar to the presentation on the container label and Prescribing Information. For example, 150 mg fosaprepitant in 50 mL (3 mg/mL)
2.	The usage of symbols (-) are noted in the storage statement, “Store	The usage of symbols may cause misinterpretation and confusion.[b]	Replace the symbols with their intended meaning.

[a]Institute for Safe medication practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Safe Alert Acute Care. 2010;15(16):1-3.

[b]ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Focinvez vials in the refrigerator at 2°C-8°C (36°F-46°F)."		
3.	The statements under storage subsection lack readability.	Lack of readability may lead to confusion of storage information for the healthcare providers.	Consider bulleting the statements under storage subsection.
Patient Information			
1.	The abbreviation "IV" is identified.	The usage of abbreviation can cause misinterpretation and confusion.[b]	Replace the abbreviation with its intended meaning.

6 RECOMMENDATIONS FOR SPES PHARMACEUTICALS INC.

Table 3. Identified Issues and Recommendations for Spes Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As currently displayed, the concentration statement (3 mg/mL) in the blue box lacks sufficient prominence.	We note, your response dated February 1, 2022, to our Information Request sent on January 24, 2022. We acknowledged that you have prominently highlighted the product strength and concentration, but the prominence of the concentration statement is not adequate on the carton labeling and container labeling.	We recommend that you add the following statement in a bright yellow color blocking on the PDP: Attention: This is a ready-to-use formulation of fosaprepitant (3 mg/mL). Fosaprepitant is available in different concentrations. And delete the separate [redacted] (b) (4) from the PDP.

Table 3. Identified Issues and Recommendations for Spes Pharmaceuticals Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The established name does not appear to be at least ½ the size of the proprietary name.	The size of the established name does not appear to comply with 21 CFR 201.10(g)(2).	Ensure the established name is at least ½ the size of the proprietary name as required per 21 CFR 201.10(g)(2).
3.	Route of administration statement includes the word [redacted] (b) (4)	[redacted] (b) (4)	Revise route of administration statement to read "For intravenous use".
4.	The NDC number especially the middle four number (product code) is overtly prominent.	Increased prominence of NDC number takes readers' attention away from other important information. The most important information on the PDP should be proprietary and established names, strength, route of administration, dosage form, and the ready-to-use statement.	Decrease the prominence of the NDC number by decreasing the font size.
5.	The net quantity statement is missing from the PDP (Principal Display Panel).	21 CFR 201.51	Add a net quantity statement to the PDP of the carton labeling and container label. The net quantity statement should be away from the strength and has less prominence to avoid confusion with the product strength statement.
6.	Usual Dosage statement terminology is inconsistent with that	21 CFR 201.55	To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4):

Table 3. Identified Issues and Recommendations for Spes Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	used in the Prescribing Information.		(b) (4)” to read “Recommended Dosage: See Prescribing Information.”
7.	The storage sentence about vial in original carton can be kept in room temperature up to 90 days is different between PI and carton labeling and container labels.	Inconsistencies between PI and labels and labeling may lead to confusion of storage information of the product.	Revise the storage statement to align across all label and labeling.
8.	The lot number statement is missing.	The lot number statement is required as per 21 CFR 201.10(i)(1).	Display the intended placement of the lot number statement.
9.	The expiration date is missing.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Display the intended placement of the expiration date and identify the format as recommended below: 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

Table 3. Identified Issues and Recommendations for Spes Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			space be used to separate the portions of the expiration date.
Container Label(s)			
1.	The negative statement (b) (4) [redacted] is found on the side panel.	The PDP clearly states that the injection is ready-to-use. (b) (4) [redacted] Post-marketing reports have indicated that negative statements may have the opposite effect of the intended meaning because the word 'not' can be overlooked and the warning be misinterpreted as an affirmative action.[c]	Remove the statement, "(b) (4) [redacted] from the side panel. Additionally, the proposed statement, (b) (4) [redacted] recommend deletion of this statement.
2.	The "Rx only statement" is overly prominent.	The increased prominence of the "Rx only statement" takes the reader's attention away from other important information on the PDP	Decrease the prominence of the "Rx only statement".

[c] Institute for Safe medication practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Safe Alert Acute Care. 2010;15(16):1-3.

Table 3. Identified Issues and Recommendations for Spes Pharmaceuticals Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		such as established name, strength, dosage form, ready-to-use statement.	
3.	The statement, “150 mg Single Dose Vial Discard unused portion” is bolded.	Overuse of bold font may diminish its effect on prominence for other important product information.	Remove the bold font, and reduce the font size of the statement as following, “Single-dose vial-discard unused portion”.
4.	The storage statement contains dashes.	The usage of symbols and abbreviations can cause misinterpretation and confusion.[b]	Revise the statement to read “Must be refrigerated, store at 2°to 8°C (36° to 46°F).”
Carton Labeling			
1.	The negative statement, (b) (4) [redacted] is found on the Principal Display Panel (PDP).	The PDP clearly states that the injection is ready-to-use. (b) (4) [redacted] Post-marketing reports have indicated that negative statements may have the opposite effect of the intended meaning because the word ‘not’ can be overlooked and the	Remove the statement, (b) (4) [redacted] from the PDP. (b) (4) [redacted] recommend deletion of this statement.

Reference ID: 5028254

Table 3. Identified Issues and Recommendations for Spes Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		warning be misinterpreted as an affirmative action.[c]	
2.	The storage information presented on the side panel lacks prominence and contains dashes.	We recommend to bold the storage information to minimize the risk of this information being overlooked. The usage of symbols and abbreviations can cause misinterpretation and confusion.[b]	Bold the statement "Must be refrigerated, store at 2°to 8°C (36° to 46°F)."
3.	As currently presented, there are two placeholders for barcodes (on the top panel and bottom panel) on the carton labeling.	Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers.	Please clarify the intention of having two barcodes on the carton labeling, i.e., if one is a linear barcode and the other one is a quick response (QR) code or data matrix code required by DSCSA.
4.	It is unclear where the machine-readable product identifier is located on the label.	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. Include the machine-readable data matrix barcode to the carton labeling. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]

Table 3. Identified Issues and Recommendations for Spes Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Focinvez that Spes Pharmaceuticals Inc. submitted on March 28, 2022, and the listed drug (LD, Emend for Injection[d] (NDA 22023).

Table 4. Comparison of Focinvez and Emend for Injection		
Product Name	Focinvez	Focinvez
Initial Approval Date	N/A	January 25, 2008
Active Ingredient	fosaprepitant	
Indication	Fosaprepitant Injection is indicated in adults and pediatric patients 6 months of age and older, in combination with other antiemetic agents, for the prevention of): acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).	
Route of Administration	intravenous	
Dosage Form	injection (ready-to-use solution)	for injection (powder)
Strength	150 mg (3 mg/mL), ready-to-use injection in a single-dose vial for intravenous infusion.	150 mg/vial (1 mg/mL)
Dose and Frequency	Adults: 150 mg Pediatric Patients 6 Months to 17 Years for the Prevention of Nausea and Vomiting Associated with Single-Day Regimens of HEC or MEC: 12 Years to 17 Years: 150 mg 2 Years to less than 12 Years: 4 mg/kg (maximum dose 150 mg) 6 Months to less than 2 Years: 5 mg/kg (maximum dose 150 mg) Pediatric Patients 6 Months to 17 Years for the Prevention of Nausea and Vomiting Associated with Single-Day Regimens of HEC or MEC: 12 Years to 17 Years 150 mg	

[d] Prescribing Information. Daily Med. Accessed on March 12, 2022.

	2 Years to less than 12 Years 4 mg/kg (maximum dose 150 mg) intravenously over 60 minutes 6 Months to less than 2 Years: 5 mg/kg (maximum dose 150 mg)	
How Supplied	Single-dose vial containing 150 mg of fosaprepitant as a clear and colorless ready-to-use injection. Supplied as follows: 1 vial per carton.	Single-dose glass vial containing 150 mg of fosaprepitant as a white to off-white lyophilized powder for reconstitution. Supplied as follows:1 vial per carton.
Storage	Store Fosaprepitant Injection vials in the refrigerator at 2°C-8°C (36°F-46°F). Fosaprepitant Injection vials, in its original carton, can be kept at room temperature, (b) (4) [redacted] for a total of 90 days.	Emend for injection vials must be refrigerated, store at 2°C-8°C (36°F-46°F). The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)]. Discard unused portion.

APPENDIX D. INFORMATION REQUEST AND RESPONSE FROM SPES PHARMACEUTICALS

FDA information request dated January 24, 2022 and responses from Spes Pharmaceuticals dated February 1, 2022.

\\CDSESUB1\evsprod\nda216686\0002\m1\us\116-risk-management-plan\116-risk-man.pdf

(b) (4)

[redacted]

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APPENDIX F. LABELS AND LABELING

F.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 Focinvez labels and labeling submitted by Spes Pharmaceuticals Inc.

- Container label received on March 28, 2022
- Carton labeling received on March 28, 2022
- Patient Information received on March 28, 2022, available from \\CDSESUB1\evsprod\nda216686\0006\m1\us\114-labeling\draft\labeling\focinvez-ppi.docx
- Prescribing Information (Image not shown) received on March 28, 2021, available from \\CDSESUB1\evsprod\nda216686\0006\m1\us\114-labeling\draft\labeling\fosap-inj-uspi.docx

F.2 Label and Labeling Images

Container label(s)

(b) (4)

[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 Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Memo

Date:	March 9, 2022
Reviewer:	Jamie Ridley Klucken, PharmD, MBA, BCPS, BCACP, Safety Evaluator, Division of Pharmacovigilance I (DPV-I)
Team Leader:	Lisa Wolf, PharmD, BCCCP DPV-I
Deputy Division Director:	CDR Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name:	Fosaprepitant Injection (fosaprepitant dimeglumine)
Subject:	Overdosage in pediatrics
Application Type/Number:	NDA 216686
Applicant:	SPES Pharmaceuticals Inc.
OSE RCM #:	2022-323

We would like to acknowledge and thank Dr. Jenni Lee for her contribution as an immunology consult on this memo.

TABLE OF CONTENTS

1 INTRODUCTION

This pharmacovigilance memo, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology (DG), contains an analysis of all adverse events associated with overdosage of fosaprepitant in the pediatric population identified in the FDA Adverse Event Reporting System (FAERS) database and the medical literature. This review will inform DG as they conduct a standard review of a literature-based 505(b)(2) New Drug Application (NDA) for Fosaprepitant Injection submitted by the applicant, SPES, to FDA on December 10, 2021.[1]

1.1 BACKGROUND AND REGULATORY HISTORY

Emend for Injection (fosaprepitant dimeglumine, NDA 022023)[a] was approved on January 25, 2008, as an intravenous (IV) antiemetic. Fosaprepitant dimeglumine is a prodrug of aprepitant[b], a substance P/neurokinin 1 (NK_1) receptor antagonist, which inhibits emesis induced by cytotoxic chemotherapeutic agents and augments the antiemetic activity of serotonin ($5\text{-}HT_3$) receptor antagonist, ondansetron, and corticosteroid, dexamethasone. Emend is indicated for use in adults and pediatric patients 6 months of age and older, in combination with other antiemetic agents, for the prevention of:

- Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- Delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).[2]

Fosaprepitant Injection (fosaprepitant dimeglumine, NDA 216686) was submitted as a 505(b)(2) NDA with the same indication as Emend.[3] The applicant is using Emend for Injection (fosaprepitant dimeglumine, NDA 022023) as the reference listed drug (RLD), as it contains the same active moiety. Emend for Injection comes in a lyophilized powder that requires reconstitution (final concentration 1 mg/mL) whereas Fosaprepitant Injection comes as a single-dose solution (3 mg/mL) ready for IV infusion. The recommended dosing for the RLD and proposed NDA in adults and pediatric patients are summarized in **Table 1** and **Table 2**, respectively.

Table 1: Recommended Dosing for Injectable Fosaprepitant Products in Adults for Prevention of Nausea and Vomiting Associated with HEC or MEC

Product Name	Formulation	Adult Dosing Recommendation
Emend	150 mg lyophilized powder in a single-dose glass vial for reconstitution (1 mg/mL)*	150 mg IV (150 mL) over 20-30 minutes
Fosaprepitant Injection	150 mg/50 mL single-dose solution ready for IV infusion (3 mg/mL)	150 mg IV (50 mL) over 20-30 minutes
* Emend must be reconstituted with 5 mL 0.9% Sodium Chloride Injection and added to an infusion bag filled with 145 mL of 0.9% Sodium Chloride Injection for a total volume of 150 mL and a final concentration of 1 mg/mL.		

[a] Generic formulations include ANDAs 203939, 204015, 204025, 205020, 206197, 209965, 210064, 210625, 210689, 211160, 211624, 211860, 212143, 212309, 212957, 213106, 213199, 214616.
[b] Aprepitant is available as an oral capsule (NDAs 021549, 209296; ANDAs 090999, 207777, 211835), oral suspension (NDA 207865), and IV emulsion (NDA 209296).

Table 2: Recommended Dosing for Injectable Fosaprepitant Products in Pediatric Patients (6 Months to 17 Years) for Prevention of Nausea and Vomiting Associated with HEC or MEC

Product Name/ Formulation	**Dosing Recommendation**		
	6 Months to < 2 Years	**2 Years to < 12 Years**	**12 to 17 Years**
Single Dose Regimen			
Emend 150 mg (1 mg/mL)[*]	5 mg/kg IV over 60 minutes (max dose 150 mg)	4 mg/kg IV over 60 minutes (max dose 150 mg)	150 mg IV (150 mL) over 30 minutes
Fosaprepitant Injection 150 mg/50 mL (3 mg/mL)	5 mg/kg IV over 60 minutes (max dose 150 mg)	4 mg/kg IV over 60 minutes (max dose 150 mg)	150 mg IV (50 mL) over 30 minutes
3-Day Dosage Regimen[†]			
Emend 150 mg (1 mg/mL)[*]	3 mg/kg IV over 60 minutes (max dose 115 mg)		115 mg IV (115 mL) over 30 minutes
Fosaprepitant Injection 150 mg/50 mL (3 mg/mL)	3 mg/kg IV over 60 minutes (max dose 115 mg)		115 mg IV (38.33 mL) over 30 minutes
* Emend must be reconstituted with 5 mL 0.9% Sodium Chloride Injection and added to an infusion bag filled with 145 mL of 0.9% Sodium Chloride Injection for a total volume of 150 mL and a final concentration of 1 mg/mL. † Fosaprepitant IV given on Day 1 followed by aprepitant oral capsules or suspension on Days 2 and 3.			

DG consulted DPV-I on January 31, 2022, to evaluate the risk of overdose in pediatric patients given the different dosage forms, concentrations, and total volume of the RLD compared to the proposed product, as they review the proposed product labeling submitted as part of the 505(b)2 NDA submission for Fosaprepitant Injection.

As part of the 505(b)(2) NDA submission, the applicant for the proposed product conducted an analysis of adverse events associated with IV fosaprepitant exposure reported to FAERS from March 6, 2008, through August 4, 2021. They did a high-level overview of the 1,365 reports retrieved and did not identify adverse events suggesting a change to labeling is needed. Notably, less than 3% (n=29) of the FAERS reports retrieved were in children less than 18 years of age.[4]

1.2 RELEVANT PRODUCT LABELING

Select sections from the applicant's proposed product labeling for Fosaprepitant Injection, applicable to the current consult, are reproduced below. Of note, in Section 6.1, there is mention of 70 pediatric patients who received a single, higher-than-recommended dose; this information is also contained in the RLD labeling. In addition, the OVERDOSAGE section of the oral aprepitant labeling describes "drowsiness and headache were reported in one patient who ingested 1440 mg of EMEND (approximately 11 times the maximum recommended single dose)."[5]

(b) (4)

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(b) (4)

2 METHODS AND MATERIALS

We used the data sources outlined in **Sections 2.1-2.2** to identify cases in which patients received higher-than-recommended dosages of IV fosaprepitant. Although the consult asked for cases in the pediatric population only, we expanded our search to all ages for completeness. Identified cases are described in **Section 3**.

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in **Table 3**.

Table 3. FAERS Search Strategy*	
Date of search	February 10, 2022
Time period of search	All reports through February 9, 2022
Search type	Quick Query
Product active ingredients	FOSAPREPITANT, FOSAPREPITANT DIMEGLUMINE, FOSAPREPITANT OR FOSAPREPITANT DIMEGLUMINE
Additional search terms†	High Level Terms: Overdoses NEC, Product administration errors and issues, Product prescribing errors and issues, Intentional product misuses, Accidental exposures to product
* See Appendix A for a description of the FAERS database. † We searched for High Level Terms “Overdoses NEC” (includes PTs Overdose, Intentional overdose, and Prescribed overdose), “Product administration errors and issues” (includes PTs Accidental overdose, Incorrect dose administered, Incorrect dosage administered, and Inappropriate schedule of product administration), “Product prescribing errors and issues (includes PTs Product prescribing error, and Product prescribing issue), “Intentional product misuses” (includes PTs Intentional product misuse and Intentional product misuse to child”), and “Accidental exposures to product” (accidental exposure to product, accidental exposure to product by child). We also searched the structured field “Dosage” to identify higher-than recommended dosages.	

2.2 LITERATURE SEARCH STRATEGY

DPV searched the medical literature with the strategy described in Table 4.

Table 4. Literature Search Strategy	
Date of search	February 16, 2022
Database	1. Embase 2. PubMed@FDA 3. Google Scholar

Table 4. Literature Search Strategy	
Search terms	1. (('fosaprepitant'/exp OR fosaprepitant) AND ('pediatrics'/exp OR pediatrics) OR (('fosaprepitant'/exp OR fosaprepitant) AND ('drug overdose'/exp OR 'drug overdose'))) AND ('adverse event'/exp OR 'adverse event' OR 'medication error'/exp OR 'medication error') 2. fosaprepitant AND pediatrics 3. "fosaprepitant" AND ("pediatrics" OR "overdose") AND "case report"

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 1,407 reports, of which 1,055 involved adult patients (18 years and older) and 31[c] involved pediatric patients (less than 18-years-old); the remaining 321 reports did not specify the patient age[d]. After a targeted review of the reports[e], we identified five cases in which patients received higher-than-recommended dosages of fosaprepitant. Only two cases, involving single higher-than-recommended doses of fosaprepitant, described resultant adverse events, one of which occurred in a pediatric patient. The remaining three cases did not report adverse events. The five cases are summarized below.

<u>Cases describing an adverse event</u>

FAERS Case #18231796, life threatening/other serious outcome, RUS, 2020
This case describes a 9-year-old female (23 kg) who received Emend IV 150 mg (rate not specified) for antiemetic supportive care. Three minutes after starting the infusion, she developed difficulty breathing, decreased oxygen saturation (83%), decreased blood pressure (71/30), and a draining hemorrhagic rash all over her body. The infusion was stopped and oxygen 2 L/min through nasal cannula was initiated along with dexamethasone 8 mg IV, clemastine 0.5 mL IV, saline 20 mL/kg for 30 minutes, and adrenaline 0.2 mL IV. The patient improved with increased blood pressure and normalization of oxygen saturation. Concomitant medications included multiple antibiotics, antifungals, granulocyte colony-stimulating factors, morphine, and cyclosporine.

Reviewer comment: This pediatric patient received a 1.6-fold overdose of fosaprepitant.

FAERS Case #8264952, other serious outcome, USA, 2011
A nurse reported a 50-year-old male received a first infusion of fosaprepitant dimeglumine 500 mg IV as an antiemetic for lung cancer chemotherapy. After 5 minutes of the fosaprepitant

[c] Of the 31 pediatric reports, 29 included patient ages in the structured field (matching the applicant's search); we identified 2 additional pediatric reports with patient age reported in the narrative. Five pediatric reports were duplicates.
[d] The structured field for age was blank and the narrative did not describe an age.
[e] We reviewed the reports retrieved from the additional search terms in **Table 3**.

infusion, the patient experienced shortness of breath, facial flushing, redness of the eyes, and oxygen saturation of 88%, and he felt like he was going to pass out. The infusion was discontinued; the patient was given nasal oxygen (3 L), hydrocortisone sodium succinate, diphenhydramine hydrochloride, and normal saline. Symptoms resolved within 5 to 10 minutes.

Reviewer comment: This adult patient received a 3.33-fold overdose of fosaprepitant.

Cases without an adverse event

FAERS Case #16369199, nonserious, USA, 2019
A consumer reported a patient of unknown age and gender received two doses of fosaprepitant 300 mg IV 3 days apart. No adverse events were reported.

FAERS Case #11703779, nonserious, USA, 2015
A pharmacist reported a 68-year-old female received fosaprepitant 150 mg IV. The next day, the patient was inadvertently given a second infusion of fosaprepitant 150 mg and oral aprepitant 80 mg. The patient denied any adverse events.

FAERS Case #9148515, nonserious, USA, 2013
A pharmacist reported a patient of unknown age and gender was prescribed fosaprepitant 150 mg IV for 5 consecutive days; the patient did not have any symptoms.

3.2 LITERATURE SEARCH

We did not identify any literature cases of adverse events associated with higher-than-recommended dosages of fosaprepitant in pediatric patients.

4 REVIEWER COMMENTS

DPV-I evaluated the FAERS database and medical literature for the risk of overdose with fosaprepitant in all patients given the different dosage form, concentration, and total volume of the RLD compared to the proposed 505(b)2 NDA Fosaprepitant Injection product. There is concern that a 3-fold overdose could occur with administration of the proposed product because of the higher concentration (3 mg/mL) compared to the RLD when reconstituted (1 mg/mL).

DPV-I retrieved one pediatric case (1.6-fold overdose) and one adult case (3.33-fold overdose) describing hypersensitivity reactions following a single, higher-than-recommended dose of IV fosaprepitant. Hypersensitivity reactions are currently listed in the WARNINGS AND PRECAUTIONS of the proposed labeling.

Dose-related reactions are often related to drug toxicity, while hypersensitivity reactions are generally considered to be independent of the dose once a low threshold dose has been exceeded.[6,7] However, drugs have been known to cause dose-dependent anaphylaxis-like reactions, without prior drug sensitization, through non-immunoglobulin E (IgE) mediated direct mast cell activation via activation of specific G-protein coupled receptors (GPCRs).[8] Studies have suggested that substance P activates mast cells through Mas-related GPCRs.[9,10] However, fosaprepitant is a substance P/NK_1 receptor <u>antagonist</u>.

We also retrieved three cases that did not describe adverse events following higher-than-recommended dosages of fosaprepitant (i.e., fosaprepitant 300 mg IV 3 days apart in a patient of unknown age, fosaprepitant 150 mg IV on day 1 and day 2 plus aprepitant 80 mg on day 2 in a 68-year-old female, fosaprepitant 150 mg IV for 5 consecutive days in a patient of unknown age).

It is reassuring that no adverse events were reported, besides known hypersensitivity reactions (n=2), despite higher-than-recommended dosages received. Additionally, the OVERDOSAGE section of oral aprepitant labeling describes minor adverse events (i.e., drowsiness and headache) despite ingestion of 1440 mg of oral aprepitant (approximately 11 times the maximum recommended single dose).

Section 6.1 of the proposed and RLD labeling describes a safety analysis where 70 pediatric patients received a single, higher-than-recommended dose of fosaprepitant. No additional information is provided, but it may be useful to review this data to inform the current safety issue.

We are mindful of the fact that the absence of reporting does not necessarily mean the absence of a signal and that FAERS data has limitations as FDA does not receive all adverse event reports that may potentially occur with a product. Additionally, many reports describing adverse events do not contain adequate information to assess for causality.

5 APPENDICES

5.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6 REFERENCES

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