CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213407Orig1s000

OTHER REVIEW(S)

MEMORANDUM

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

Date of This Memorandum:	April 15, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 213407
Product Name and Strength:	Emerphed (ephedrine sulfate) injection, 50 mg/10 mL
Applicant/Sponsor Name:	Nexus Pharmaceuticals Inc.
OSE RCM #:	2019-1217-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received via email on April 14, 2020 for Emerphed. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels and carton labeling for Emerphed (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] and email communications between the Office of New Drugs (OND) Project Manager and Nexus.

2 DISCUSSION

In our previous label and labeling review, we recommended that Nexus remove the "in 0.9% sodium chloride" from the drug product name because diluents are not routinely included in drug product names for products that are in vials. We also recommended that Nexus replace the statement "(b) (4)" with "(b) (4) – Do not dilute" and remove "(b) (4)" from the container label and carton labeling because this was not a standard dosage form. In response to our recommendations, Nexus expressed concern with removing "(b) (4)" and "0.9% sodium chloride". They were concerned

[a] Johnson, C. Label and Labeling Review for Emerphed (NDA 213407). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 20. RCM No.: 2019-1217.

that removal of the text indicated above would lead to their product being confused with the currently marketed concentrated drug product that requires dilution prior to administration. To address their concern, we proposed that Nexus replace the statement "(b) (4) " with "Premixed formulation – Do not dilute" on the container label and carton labeling. We also proposed that Nexus consider adding a flag to the carton labeling with the statement "Premixed formulation – Do not dilute".

3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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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: March 30, 2020

To: Alla Bazini, M.D.
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Kimberly Compton, Regulatory Project Manager
Division of Regulatory, Operations for Neuroscience

Lisa Basham, Associate Director for Labeling, (DAAP)

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for EMERPHED (ephedrine sulphate injection) for intravenous use

NDA: 213407

In response to DAAP's consult request dated March 30, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for EMERPHED (ephedrine sulphate injection) for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAP on March 24, 2020, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on January 8, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Koung Lee at (240) 402-8686 or Koung.lee@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:	February 20, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 213407
Product Name and Strength:	Emerphed (ephedrine sulfate) injection, 5 mg/mL
Total Product Strength:	50 mg/10 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Nexus Pharmaceuticals Inc.
FDA Received Date:	September 27, 2019 and December 13, 2019 and January 8, 2020
OSE RCM #:	2019-1217
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Emerphed (ephedrine sulfate) injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Emerphed Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

NDA 213407 is a 505(b)(2) NDA and the listed drug product is Akovaz, NDA 208289.

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

4 FINDINGS AND RECOMMENDATIONS

While reviewing the proposed container label, carton labeling and prescribing information, we noted that the formulation does not require dilution prior to administration and that currently marketed ephedrine products require dilution prior to administration. We sent an information request (IR) to Nexus to request their intended communication plan to alert users that their ephedrine sulfate product dose not require dilution. In their response, Nexus submitted a proposed sales aid (Appendix G) as well as a revised container label and carton labeling[a] and

[a] Cover Letter (NDA 213407 for Emerphed). Lincolnshire (IL): Nexus Pharmaceuticals, Inc. 2020 JAN 08. Available from: \\cdsesub1\evsprod\nda213407\0016\m1\us\cover-letters\cover-letter-0016.pdf

stated that the promotional materials would be sent to all USA hospitals. Furthermore, Nexus stated that, "As you can see from the two documents a statement [redacted]' is printed on the carton and '[redacted]' as well as [redacted]' in Sales Aid." We agree with the Applicant's plan to alert healthcare providers through the use of promotional materials. We also agree that it will be helpful to include the statement that the product should not be diluted on the container labels and carton labeling. While we do not routinely review promotional sales aides we do not agree that the term '[redacted]' is appropriate [redacted]

We also noted that the container labels and carton labeling include the dosage form as "[redacted]" and the product name as "ephedrine sulfate [redacted]". We consulted with the Office of Pharmaceutical Quality (OPQ) reviewer to confirm that the dosage form "[redacted]" was not a standard dosage form [redacted] included as part of the product name for products that are available in vials. We shared with OPQ that we planned to recommend that the Applicant remove the statement "[redacted]" and revise the product name to "ephedrine sulfate injection" on the container label and carton labeling. OPQ did not object to our plan. We have included our recommendations in Table 3 below for Nexus.

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), container label, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Sales Aid			
1.	The sales aid that was submitted via email on December 13, 2020 contains the statement "[redacted]".	The statement "[redacted]	We defer to the Office of Prescription Drug Promotion (OPDP) to assess the acceptability of the sales aid. We suggest that a more appropriate description of this

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(b) (4)	product is "(b) (4)".
General Issues – Prescribing Information			
1.	The product name is listed as "Ephedrine Sulfate (b) (4) throughout the Prescribing Information (PI) as a placeholder for the proprietary name.	We reference our proprietary name review for NDA 213407 dated October 16, 2019, concluding that the proprietary name, Emerphed, was found conditionally acceptable.	Revise the Prescribing Information to include the conditionally acceptable proprietary name, Emerphed.
General Issues – Prescribing Information			
1.	In the Dosage and Administration section of the Highlights and Full Prescribing Information, some of the doses do not contain the associated units of measure (mg) immediately following them. For example "5 to 10 mg".	All necessary dosage information must be present in proper format in order to prevent medication errors. If the unit of measure does not immediately follow the numeral, the lower dose in the dosage range may be overlooked.	Add the unit of measure, "mg", after the numeral "5" so that the statement reads "5 mg to 10 mg".
Highlights of Prescribing Information			
1.	The Dosage and Administration section contains the statement "(b) (4)".	While this appears to be a typographical error, it should be revised.	Revise the statement to read "Do not dilute before administration."
2.	In the Dosage Forms and Strengths section, the package type is	"Single (b) (4)" is not a recommended package type term and is inconsistent with the	If OPQ concurs, to maintain consistency with the package type term that is on the PDP

	described as "(b) (4) ".	package type term "single-dose" that is located on the container label, carton labeling and elsewhere in the Prescribing Information (PI).	and throughout the PI, revise "(b) (4)" to "single dose".
Full Prescribing Information – Section 2 Dosage and Administration			
1.	(b) (4)		
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The color of the solution has been omitted.	Per 21 CFR 201.57(c)(4)(ii), this section should include all of the appropriate information to facilitate identification of the dosage form.	Add the color of the solution to this section. For example, "Ephedrine sulfate…is a clear, colorless solution available as a single-dose…".
2.	The total quantity per total volume has been omitted.	The total quantity per total volume should be included to reduce the risk of misinterpretation and dosing errors.	Add the total quantity per total volume, 50 mg/10 mL, to the Dosage Forms and Strengths section.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The package type is described as "(b) (4) ".	"(b) (4)" is not a recommended package type term and is inconsistent with the package type term "single dose" that is located on the container label, carton labeling and elsewhere in the Prescribing Information (PI).	If OPQ concurs, to maintain consistency with the package type term that is on the container label, carton labeling and elsewhere in the PI, revise "(b) (4)" to "single dose".
2.	The total quantity per total volume and color of	Per 21 CFR 201.57(c)(17), this section should include all of the appropriate	Add the total quantity per total volume and color of the solution to this section. For

	the solution have been omitted.	information to facilitate identification of the dosage form.	example, "Ephedrine sulfate… 50 mg/10 mL (5 mg/mL) is a clear, colorless solution and is supplied as follows…".
3.	The product is described as "(b) (4)".	The inclusion of statements such as "(b) (4)" in product labeling may not be accurate (b) (4)	We defer to OPQ to determine the appropriateness of this statement.

Table 3. Identified Issues and Recommendations for Nexus Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The total quantity per total volume and quantity per milliliter (mL) is presented as "50 mg/10 mL (5 mg per 1 mL)" on the container label and as "50 mg per 10 mL (5 mg per 1 mL)" on the carton labeling.	The presentation of the total quantity per total volume and quantity per mL should be consistent throughout all labels and labeling.[c]	Revise the concentration per mL on the container label from "(5 mg per 1 mL)" to "(5 mg/mL)". Furthermore, revise the total quantity per total volume and concentration per mL on the carton labeling from "50 mg per 10 mL (5 mg per 1

(b) (4)

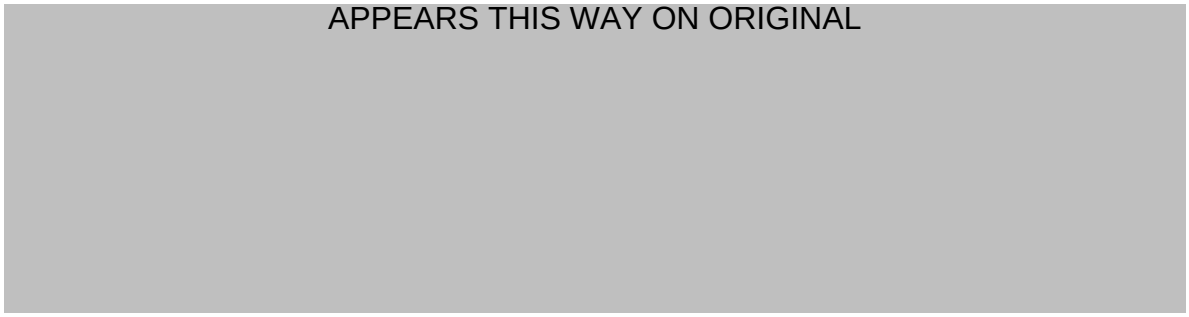
[c] United States Pharmacopoeia (USP) General Chapter <7> Labeling

Table 3. Identified Issues and Recommendations for Nexus Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			mL)" to "50 mg/10 mL (5 mg/mL)".
2.	(b) (4)		
3.	The format for expiration date is not defined on the container label or carton labeling.	The format of the expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date 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.
4.	(b) (4)		

Table 3. Identified Issues and Recommendations for Nexus Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	[redacted] (b) (4)		drug product name and include parentheses around the established name so that it reads as: Emerphed (ephedrine sulfate) Injection
5.	The dosage form is included as "[redacted] (b) (4) ".	"[redacted] (b) (4) " is not a standard dosage form.	Remove the statement "[redacted] (b) (4) ".
Carton Labeling			
1.	[redacted] (b) (4) " is listed immediately beneath the proprietary name on the principal display panel, top panel, and right side panel.	"[redacted] (b) (4) " is not a standard dosage form [redacted] (b) (4)	Remove the statement "[redacted] (b) (4) . Also, see recommendation #5 Container Label and Carton Labeling section above.
2.	The net quantity on the carton labeling is included as "10 x 10 mL single dose vials" while the net quantity in the How Supplied/Storage and Handling section of the Prescribing Information is included as "10 mL vials packaged in a carton of [redacted] (b) (4) ".	Inconsistent net quantity information can lead to confusion during ordering and distribution of the drug product.	Clarify the net quantity of the carton labeling. If the proposed net quantity is not 10 vials please revise the carton labeling to reflect the appropriate number of vials per carton.

5 CONCLUSION

Our evaluation of the proposed Emerphed Prescribing Information (PI), container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Nexus Pharmaceuticals Inc. so that recommendations are implemented prior to approval of this NDA.



APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Emerphed that Nexus Pharmaceuticals Inc. submitted on September 27, 2019, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Emerphed		
Product Name	Akovaz	Emerphed
Initial Approval Date	August 1, 2016	N/A
Active Ingredient	Ephedrine sulfate	same
Indication	treatment of clinically important hypotension occurring in the setting of anesthesia	same
Route of Administration	Intravenous bolus	same
Dosage Form	injection	same
Strength	50 mg/mL	50 mg/10 mL (5 mg/mL)
Dose and Frequency	5 mg to 10 mg as needed not to exceed 50 mg (dilute before administration)	5 mg to 10 mg as needed not to exceed 50 mg (Do not dilute before administration)
How Supplied	1 mL Single-dose vial supplied in packages of 25	10 mL single-dose vial supplied in carton of (b) (4)
Storage	Controlled room temperature	same
Container Closure	vial	same

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 25, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, ephedrine . Our search did not identify any previous reviews.

APPENDIX C. – N/A

APPENDIX D. – N/A

APPENDIX E. – N/A

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,[d] along with postmarket medication error data, we reviewed the following Emerphed labels and labeling submitted by Nexus Pharmaceuticals Inc.

- Container label received on January 8, 2020
- Carton labeling received on January 8, 2020
- Prescribing Information (Image not shown) received on September 27, 2019 can be accessed in EDR via:
    - o \\cdsesub1\evsprod\nda213407\0008\m1\us\labeling\revised-ephedrine-sulfate-pi-labeling.docx

F.2 Label and Labeling Images

Container label

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

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