

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213994Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: September 29, 2020

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

Kimberly Compton, Regulatory Project Manager, (DAAP)

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 Ephedrine Sulfate Injection for intravenous use

NDA: 213994

In response to DAAP's consult request dated April 28, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for ephedrine sulfate injection.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on September 22, 2020 and have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 3, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Koung Lee at (301) 402-8686 or Koung.lee@fda.hhs.gov.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

KOUNG U LEE
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic,
and Reproductive Medicine
Division of Pediatric and Maternal Health
Silver Spring, MD 20993

MEMORANDUM TO FILE

Date of Consult Request: August 26, 2020

From: Denise N. Johnson-Lyles, Ph.D.
Senior Regulatory Project Manager
Division of Regulatory Operations for Rare Diseases,
Pediatrics, Urologic, and Reproductive Medicine

Subject: Labeling consult request

NDA Number: NDA 213994
Application Type: 505(b)(2)

Drug: Ephedrine Sulfate Injection, 5 mg/mL

Applicant: Nevakar, Inc.

Indication(s): Treatment of clinically important hypotension occurring in
the setting of anesthesia

The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) submitted a consult request to the Division of Pediatric and Maternal Health (DPMH) on August 26, 2020, asking for assistance with the review of labeling language included in the Prescribing Information (PI) for the above referenced application. Specifically, DPMH (maternal health and pediatric teams) was requested to assist with the review of Section 8 of the PI, given noted differences in this section compared to the PI of the listed drug (LD), Akovaz (NDA 208289).

DPMH participated in a team meeting on September 3, 2020 and provided labeling recommendations to DAAP for subsequent negotiation with the applicant. DPMH recommends that the labeling language in Section 8 of the PI for this application remain consistent with the language provided in this section for the most recently approved PI of the LD, Akovaz (approved on April 8, 2020). There are no further comments at this time.

This memorandum will close out the consult request.

RPM for DPMH- Denise Johnson-Lyles
Chief Project Manager for DPMH – George Greeley
DPMH Maternal Health Reviewer- Christos Mastroyannis
DPMH Maternal Health Team Leader- Tamara Johnson
DPMH Pediatric Team Reviewer – Shamir Tuchman
DPMH Pediatric Team Leader – Mona Khurana
DPMH Deputy Division Director – John Alexander
DPMH Division Director- Lynne Yao

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/s/

DENISE N JOHNSON-LYLES
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RPM for DPMH Closeout

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

Date of This Memorandum:	August 19, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 213994
Product Name and Strength:	Ephedrine sulfate injection, 5 mg/mL
Total Product Strength:	50 mg/10 mL
Applicant/Sponsor Name:	Nevakar, Inc.
OSE RCM #:	2019-2634
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label and carton labeling received on August 3, 2020 for ephedrine sulfate. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for ephedrine sulfate (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.

^a Johnson, C. Label and Labeling Review for ephedrine sulfate (NDA 213994). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 05. RCM No.: 2019-2634.

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/s/

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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:	May 20, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 213994
Product Name and Strength:	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:	Nevakar, Inc.
FDA Received Date:	December 18, 2019 and March 19, 2020
OSE RCM #:	2019-2634
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ephedrine sulfate injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Ephedrine sulfate prescribing information (PI), 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
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

3 FINDINGS AND RECOMMENDATIONS

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
Prescribing Information – General Issues			
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)	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	Add the unit of measure, “mg”, after the numeral “5” so that the statement reads “5 mg to 10 mg”.

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

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	immediately following the numeral. For example “5 to 10 mg”.	numeral, the lower dose in the dosage range may be overlooked.	
2.	The statement “ready-to-use” is included in the Dosage Forms and Strengths section of the Highlights and Full Prescribing Information.	The statement “ready-to-use” may be misinterpreted and we have included a recommendation below to include the term “Ready to Use formulation” in section 2.1 of the PI.	Remove the term “ready-to-use” from the Dosage Forms and Strengths section of the Highlights and Full Prescribing Information
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Section 2.1 “General Dosage and Administration Instructions” does not include a description that this product does not require dilution.	This is important administration information and should be included before the basic dosing information in the Dosage and Administration section so that users are aware that this product does not require dilution.	Add the statement “Ready to Use formulation. Do not dilute” to section 2.1 of the Prescribing Information.
2.	The PI includes Section 2.3, entitled “Prepare a 5 mg/mL Solution for bolus Intravenous Administration”.	This product is a “ready to use formulation” that does not require preparation. Inclusion of this section could lead to confusion which may result in medication errors.	Delete section 2.3 from the Prescribing Information.
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The color of the solution has not been included in the Dosage Forms and Strengths section of the Full Prescribing Information.	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...”.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The package type is described as “single use”.	“Single-use” 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 “single use” to “single dose”.
2.	The total quantity per total volume and color of the solution have not been included.	Per 21 CFR 201.57(c)(17), this section should include all of the appropriate information to facilitate identification of the dosage form.	Add the total quantity per total volume and color of the solution to this section. For example, “Ephedrine Sulfate Injection, USP 50 mg/10 mL (5 mg/mL) is a clear, colorless solution and is supplied as follows...”.
3.	The National Drug Code (NDC) is denoted by a placeholder.	The NDC that is listed on the carton labeling should be consistent with the NDC that is listed in the How Supplied section.	We have provided a recommendation for Nevakar in the table below to submit NDC’s for the container label and carton labeling. Once Nevakar addresses our recommendation below, they should also revise the PI accordingly and resubmit for review.

Table 3. Identified Issues and Recommendations for Nevakar, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The National Drug Code (NDC) is denoted by a	Per 21 CFR 207.33, drug products subject to listing with the FDA must have a	Revise the placeholder to the actual NDC’s and submit for our review.

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

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	placeholder “XX-XXX-XXX-XXX”.	unique NDC to identify its labeler, product, and package size and type.	
2.	The container label includes the statement “Usual Dosage: See package insert.” and the carton labeling includes the statement “Dosage: See package insert.”	This statement is not consistent with the prescribing information.	Revise the container label and the carton labeling to read “Recommended Dosage: See prescribing information.”
Container Label(s)			
1.	The container label includes the statement “Ready-to-use” on the side panel. Furthermore, there is no statement that this product does not require dilution.	We note that the formulation and not the product as a whole is “Ready-To-Use”. The statement “Ready-To-Use”, may imply that the product does not require further manipulation prior to administration (i.e. withdraw correct volume from vial). A user may interpret this statement to mean that the entire contents should be withdrawn from the vial which could lead to an overdose medication error.	Revise this statement to “Ready-To-Use Formulation and does NOT require further dilution” .” and relocate to the Principal Display Panel (PDP). We recommend that you increase the prominence (i.e. color, bolding, boxing, font) of this statement as well to ensure that users can easily identify this important information.
2.	The container label does not include a lot number statement.	Lot number statement is required on the immediate container when there is sufficient space per 21 CFR 201.10(i)(1).	Add the lot number statement to the label.
3.	The container label does not include an expiration date.	Expiration date is required on the immediate container and carton labeling per 21 CFR 211.137.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you

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

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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.
Carton Labeling			
1.	The carton labeling includes the statements “Ready-To-Use” on the PDP (front panel) and back panel and “Ready-To-Use product and does not require further dilution” on the side panel.	We note that the formulation, and not the product as a whole, is “Ready-To-Use”. The statement “Ready-To-Use”, may imply that the product does not require further manipulation prior to administration (i.e. withdraw correct volume from vial). A user may interpret this statement to mean that the entire	Revise these statements to “Ready-To-Use Formulation and does NOT require further dilution.” We recommend that you increase the prominence (i.e. color, bolding, boxing, font) of this statement on the PDP (front) and back panels as well to ensure that users can easily identify this important information.

Table 3. Identified Issues and Recommendations for Nevakar, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		contents should be withdrawn from the vial which could lead to an overdose medication error.	
2.	The carton labeling does not include product identifiers.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. ^a The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

4 CONCLUSION

Our evaluation of the proposed Ephedrine sulfate 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 Nevakar, Inc. so that recommendations are implemented prior to approval of this NDA.

^a 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

Table 4 presents relevant product information for Ephedrine sulfate that Nevakar, Inc. submitted on March 19, 2020.

Table 4. Relevant Product Information for Ephedrine sulfate	
Initial Approval Date	N/A
Active Ingredient	Ephedrine sulfate
Indication	treatment of clinically important hypotension occurring in the setting of anesthesia
Route of Administration	Intravenous bolus
Dosage Form	injection
Strength	50 mg/10 mL (5 mg/mL)
Dose and Frequency	5 mg to 10 mg intravenous bolus as needed, not to exceed 50 mg
How Supplied	10 mL vial in carton
Storage	Controlled room temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 17, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 213994. Our search identified no 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,^b along with postmarket medication error data, we reviewed the following Ephedrine sulfate labels and labeling submitted by Nevakar, Inc..

- Container label(s) received on December 18, 2019
- Carton labeling received on December 18, 2019
- Prescribing Information (Image not shown) received on March 19, 2020 can be accessed in EDR via:
 - o <\\cdsesub1\evsprod\nda213994\0002\m1\us\114-labeling\draft\labeling\ephedrine-sulfate-prescribing-information-word.docx>

F.2 Label and Labeling Images

Container label



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

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