CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215700Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 6, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 215700
Product Name and Strength:	Norepinephrine in Sodium Chloride Injection, 4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL), and 16 mg/250 mL (64 mcg/mL)
Applicant/Sponsor Name:	InfoRLife SA
OSE RCM #:	2021-2251-1
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on August 29, 2022 for Norepinephrine in Sodium Chloride. We reviewed the revised container label and carton labeling for Norepinephrine in Sodium Chloride Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

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

[a] Straka, M. Label and Labeling Review for Norepinephrine in Sodium Chloride (NDA 215700). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAY 09. RCM No.: 2021-2251.

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HINA S MEHTA
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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: May 18, 2022

To: Mary Southworth, M.D., Medical Officer
Division of Cardiology and Nephrology (DCN)

Quynh M Nguyen, Regulatory Project Manager (DCN)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for NOREPINEPHRINE BITARTRATE IN SODIUM CHLORIDE injection, for intravenous use

NDA: 215700

In response to DCN's consult request dated February 15, 2022, OPDP has reviewed the proposed product labeling (PI) for NOREPINEPHRINE BITARTRATE IN SODIUM CHLORIDE injection, for intravenous use. This supplement provides for a new application indicated for restoration of blood pressure in adult patients with acute hypotensive states.

PI: OPDP's comments on the proposed labeling are based on the draft version received by electronic mail from DCN on May 10, 2022, and are provided below. OPDP does not have any additional comments at this time.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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CHARUNI P SHAH
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	May 9, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 215700
Product Name, Dosage Form, and Strength:	Norepinephrine Bitartrate in Sodium Chloride Injection, 4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL) and 16 mg/250 mL (64 mcg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	InfoRLife SA (InfoRLife)
FDA Received Date:	November 19, 2021 and February 3, 2022
OSE RCM #:	2021-2251
DMEPA 2 Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As a part of the approval process for 505(b)(2) NDA 215700 submission, this review evaluates the proposed Prescribing Information (PI) and carton and container labels for Norepinephrine Bitartrate in Sodium Chloride Injection for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

On November 19, 2021, InfoRLife submitted a 505(b)(2) NDA to obtain marketing approval for Norepinephrine Bitartrate in Sodium Chloride Injection. The Listed Drug (LD) for this product is Levophed (norepinephrine bitartrate) Injection NDA 007513. Levophed Injection is currently marketed as a 4 mg/4 mL (1 mg/mL) single-dose vial or single-dose ampule that is diluted in 1,000 mL of 5% Dextrose or 5% Dextrose/Sodium Chloride for intravenous infusion. The proposed product will be available in 4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL), and 16 mg/250 mL (64 mcg/mL) ready to use single dose bags.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note the proposed Norepinephrine Bitartrate in Sodium Chloride Injection product will have the same active ingredient, dosage form (injection), indication, route of administration (intravenous infusion), and dosing regimen as the reference listed drug, Levophed. However, there are differences in the proposed presentation as Norepinephrine Bitartrate in Sodium Chloride Injection will be available in 4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL) and 16 mg/250 mL (64 mcg/mL) as premixed, ready-to-use single dose bags.

We performed a risk assessment of the proposed prescribing information (PI), carton labeling, and container labels to identify deficiencies that may lead to medication errors and areas for improvement. We identified areas of the proposed PI, container labels, and carton labeling that could be revised to improve clarity and readability of important information. For the Division, we note the PI could be improved for clarity with respect to the dosage form and strengths, how supplied/ storage and handling, and the administration instructions. For the Applicant, we note there are a series of vertical lines as part of the label design which might be misconstrued as a barcode on the 16 mg/250 mL (64 mcg/mL), lack of prominence for the entire established name, expression of the strength statement, and lack of net quantity statement. These factors may confuse the user and inadvertently lead to medication errors.

We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 below and advise they be implemented prior to approval of NDA 215700.

4 CONCLUSION & RECOMMENDATIONS

Our review concludes the proposed PI, carton and container labels for norepinephrine bitartrate Injection may be improved to ensure safe product use. We provide specific recommendations for the Division in Section 4.1 and recommendations for InfoRLife in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. Dosage and Administration

   a. We recommend revising the first bullet to remove (b) (4) that is not needed. Revise to "Initiate at 8 to 12 mcg/min and adjust the rate to maintain blood pressure sufficient to maintain the circulation of vital organs. (2.2)".

   b. We recommend revising the second bullet to remove (b) (4) to prevent confusion. Revise to "The average maintenance dose ranges from 2 to 4 mcg/min. (2.2)".

2. Dosage Form and Strengths

   a. We recommend including the dosage form as part of the statement. Revise to read "Injection: 250 mL single-dose container with:

      - 4 mg equivalent of norepinephrine (16 mcg/mL) in 0.9% sodium chloride
      - 8 mg equivalent of norepinephrine (32 mcg/mL) in 0.9% sodium chloride
      - 16 mg equivalent of norepinephrine (64 mcg/mL) in 0.9% sodium chloride".

B. Full Prescribing Information

1. Dosage and Administration Section, 2.1 Important Dosage and Administration Instructions

a. At the end of the discontinuation section, we recommend adding "Discard unused portion" to prevent confusion.

2. Dosage Form and Strengths

   a. We recommend listing the three strengths in separate bullets for ease of readability. Revise as follows:

      "Injection: Norepinephrine in 0.9% sodium chloride is a clear, colorless premixed solution in 250 mL single-dose container as:

      - 4 mg equivalent of norepinephrine (16 mcg/mL)
      - 8 mg equivalent of norepinephrine (32 mcg/mL)
      - 16 mg equivalent of norepinephrine (64 mcg/mL)

3. How Supplied/ Storage and Handling

   a. We recommend removing the statement, (b) (4) so that Section 16 reads "Norepinephrine Bitartrate in Sodium Chloride Injection is filled in 250 mL Nexcel bags available as:" for clarity.

   b. We recommend removing (b) (4) as that information is not needed.

   c. We recommend moving the statement "Store in original carton (b) (4) to protect from light" next to the storage temperature information to ensure this important information is not missed.

4.2 RECOMMENDATIONS FOR INFORLIFE SA (INFORLIFE)

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

A. General Comments (Container labels & Carton Labeling)

1. We note that the presentation of the established name (b) (4) In addition, "Bitartrate is part of the established name. We recommend changing the font of "Bitartrate" so that "Norepinephrine" and "Bitartrate" are the same size and font.

2. As currently presented the 16 mg/250 mL strength contains red lines at the top left portion of the label. The lines may be interpreted as a barcode and if they are scanned and do not return information, the barcode scan may be overridden leading to medication errors. To prevent confusion, we recommend removing/changing the vertical lines as part of the trade dress on the 16 mg/250 mL strength.

3. We note the statement [redacted]

4. We recommend changing the statement "[redacted]" to "Check for minute leaks and solution clarity.".

5. To ensure consistency with the Prescribing Information, revise the statement, "[redacted]" to read "Recommended Dosage: See prescribing information."

6. As currently presented the strength (e.g 4 mg) is larger than the volume (i.e. 250 ml). Revise the strength statement so that it is the same size as the volume.

B. Carton Labeling

1. As currently presented the net quantity statement is on the principal display panel of the carton labeling does not state the bag size. We recommend adding the bag size to the net quantity statement (i.e. 10 x 250 mL bags) to the carton labeling to indicate the number of bags supplied in each carton.

C. Container Label

1. We recommend including the statement "[redacted]" to ensure this important information is not missed.

D. Overwrap Label

1. Revise the statement [redacted]

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Norepinephrine bitartrate received on February 3, 2022 from InfoRLife SA (InfoRLife), and the listed drug (LD).

Table 2. Relevant Product Information for Norepinephrine bitartrate and the Listed Drug

Product Name	**Norepinephrine bitartrate**	**Levophed[a]**
Initial Approval Date	N/A	July 13, 1950
Active Ingredient	Norepinephrine Bitartrate in Sodium Chloride	norepinephrine bitartrate
Indication		Levophed is indicated to raise blood pressure in adult patients with severe, acute hypotension.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL) and 16 mg/250 mL (64 mcg/mL)	4 mg/4 mL
Dose and Frequency	After an initial dosage of 8 mcg to 12 mcg per minute via intravenous infusion, assess patient response and adjust dosage to maintain desired hemodynamic effect. Monitor blood pressure every two minutes until the desired hemodynamic effect is achieved, and then monitor blood pressure every five minutes for the duration of the infusion. Typical maintenance intravenous dosage is 2 mcg to 4 mcg per minute.	After an initial dosage of 8 mcg to 12 mcg per minute via intravenous infusion, assess patient response and adjust dosage to maintain desired hemodynamic effect. Monitor blood pressure every two minutes until the desired hemodynamic effect is achieved, and then monitor blood pressure every five minutes for the duration of the infusion. Typical maintenance intravenous dosage is 2 mcg to 4 mcg per minute.
How Supplied	Packaging Configuration / Total Norepinephrine Bitartrate: 1 single-dose bag, 10 bags per carton — 4 mg/ 250 mL* (16 mcg/mL) 1 single-dose bag, 10 bags per carton — 8 mg/ 250 mL* (32 mcg/mL) 1 single-dose bag, 10 bags per carton — 16 mg/ 250 mL* (64 mcg/mL)	Strength / Package: 4 mg/ 4 mL (1 mg/mL) — 10 Vials in a carton 4 mg/ 4 mL (1 mg/mL) — 10 Ampules in a carton

	(b) (4)	
Storage	Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature.]. (b) (4)	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]. Store in original carton until time of administration to protect from light. Discard unused portion.
Container Closure	Each filled bag is packed in an overwrap with a transparent band and oxygen scavenger and oxygen indicator placed inside the overwrapping to prevent deterioration of drug product.	Levophed is a sterile, colorless solution for injection intended for intravenous use, available as 4 mg/4 mL in single-dose amber glass vials and in single-dose clear glass ampules.

[a] Levophed [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 OCT 21. Available from: https://www.accessdata fda.gov/drugsatfda_docs/label/2020/007513s045lbl.pdf.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 16, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 215700 and norepinephrine. Our search did not identify any previous reviews that are applicable to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Norepinephrine bitartrate labels and labeling submitted by InfoRLife SA (InfoRLife).

- Container label received on November 19, 2021.
- Carton labeling received on November 19, 2021.
- Prescribing Information (Image not shown) received on February 3, 2022, available from \\CDSESUB1\evsprod\nda215700\0005\m1\us\114-labeling\draft\labeling\draft-pi-pdf.pdf

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

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