CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214313Orig1s000

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:	September 8, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214313
Product Name and Strength:	Norepinephrine Bitartrate in 5% Dextrose Injection, 4 mg / 250 mL (0.016 mg/mL) and 8 mg / 250mL (0.032 mg/mL)
Applicant/Sponsor Name:	Baxter Healthcare Corporation
OSE RCM #:	2020-513-1
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Baxter submitted revised container labels and carton labeling received on September 3, 2020 for Norepinephrine Bitartrate in 5% Dextrose Injection. We reviewed the revised container labels and carton labeling for Norepinephrine Bitartrate in 5% Dextrose 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

We note Baxter confirmed the expiration date format as MM/YYYY. In addition, the statement (b) (4) was removed from all of the labeling. Baxter confirmed the smallest individual saleable unit is the shipping carton which contains 20 individual bags. The shipping carton is a tertiary package and thus not provided. Baxter confirmed the shipping carton label will contain a 2-dimentional data matrix barcode and in human readable format. Baxter implemented all of our recommendations and we have no additional recommendations at this time.

[a] Aidoo, M. Label and Labeling Review for Norepinephrine Bitartrate in 5% Dextrose Injection (NDA 214313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 17. RCM No.: 2020-513.

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MARIETTE A AIDOO
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HINA S MEHTA
09/09/2020 11:53:45 AM

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

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

Memorandum

Date: August 25, 2020

To: Quynh M. Nguyen, Pharm.D., RAC, Regulatory Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Michael Monteleone, MS, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)

From: Puja Shah, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Pharm.D., RAC, CPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for NOREPINEPHRINE BITARTRATE IN 5% DEXTROSE INJECTION, for intravenous use

NDA: 214313

In response to DRO-CHEN's consult request dated April 20, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for NOREPINEPHRINE BITARTRATE IN 5% DEXTROSE INJECTION, for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRO-CHEN (Quynh M. Nguyen) on August 18, 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 March 16, 2020, and our comments are provided below.

Thank you for your consult.

If you have any questions, please contact Puja Shah at (240) 402-5040 or puja.shah@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:	August 17, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214313
Product Name, Dosage Form, and Strength:	Norepinephrine Bitartrate in 5% Dextrose Injection , 4 mg / 250 mL (0.016 mg/mL) and 8 mg / 250mL (0.032 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Baxter Healthcare Corporation
FDA Received Date:	March 16, 2020 and July 2, 2020
OSE RCM #:	2020-513
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As a part of the approval process for 505(b)(2) NDA 214313 submission, this review evaluates the proposed Prescribing Information (PI) and container labels for Norepinephrine Bitartrate in 5% Dextrose Injection.

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

Baxter submitted a 505(b)(2) NDA to obtain marketing approval for Norepinephrine Bitartrate in 5% Dextrose Injection. The Listed Drug (LD) for this product is Levophed (norepinephrine bitartrate) Injection. Levophed Injection is currently approved as a 4 mg/4 mL (1 mg/mL) single-dose vial that is diluted in 1,000 mL of 5% Dextrose or 5% Dextrose/Sodium Chloride for intravenous infusion. We note Levophed and the proposed Norepinephrine Bitartrate in 5% Dextrose will have the same indication, route, and dosing regimen. However, there are differences in the proposed presentation as Norepinephrine Bitartrate in 5% Dextrose will be available in 4 mg/250 mL (0.016 mg/mL) and 8 mg/250 mL (0.032 mg/mL) as a premixed product in a single dose VIAFLO infusion bags.

We performed a risk assessment of the full prescribing information (PI) and container labels to identify deficiencies that may lead to medication errors and areas for improvement. For the Division, we note the PI could be improved for clarity. For the Applicant, we note inconsistency in the presentation of the strength in relation to the PI, need clarity on expiration date format, presentation of the vehicle on the label, and revision to storage information for consistency

with the PI. 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 214313.

4 CONCLUSION & RECOMMENDATIONS

Our review concludes the proposed PI and container labels for Norepinephrine Bitartrate in 5% Dextrose may be improved to ensure safe product use. We provide specific recommendations for the Division in Section 4.1 and recommendations for Baxter in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information (HPI)
    1. Dosage and Administration
        a. We recommend deleting the first four bullet points as this information is already presented in the Full PI and is not needed in this section.
    2. Dosage Forms and Strengths
        a. We recommend revising the statement as follows (b) (4) [redacted] to increase clarity.

B. Full Prescribing Information (FPI)
    1. Indications and Usage
        a. Consider streamlining bolded font or using sentence case for statements in Section 1 "NOREPINEPHRINE BITARTRATE IN 5% DEXTROSE INJECTION is indicated to raise blood pressure in adult patients with severe, acute hypotension " to improve uniform readability because sentences in all uppercase letters or inter-mixed boldening of upper and lower cases are more difficult to read.
    2. Dosage and Administration
        a. We recommend moving the statement in Section 2.1 (Administration) " (b) (4) [redacted] for particulate matter and discoloration…" to Section 2.4 to read: " (b) (4) [redacted] as the information should be present in sequence of steps completed.
        b. In section 2.1 (Administration), delete duplicate statement: " (b) (4) [redacted]

c. [redacted] (b) (4)

3. Dosage Forms and Strength Section

    a. Revise to include description of the product as follows: Injection: norepinephrine bitartrate [redacted] (b) (4) is a colorless to slightly yellow solution for intravenous infusion:

        i. [redacted] (b) (4)

        ii. [redacted]

4. How Supplied/ Storage and Handling Section

    a. In Section 16, include the [redacted] (b) (4) as part of the storage information for consistency with the carton labeling. Revise the statement "Protect from light. [redacted] (b) (4) " to read: "Protect from light. [redacted] (b) (4) " for increased clarity.

4.2 RECOMMENDATIONS FOR BAXTER HEALTHCARE CORPORATION

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

A. General Comments (CONTAINER LABEL AND CARTON LABELING)

1. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use for the expiration date. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend 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. We recommend that a hyphen or a space be used to separate the portions of the expiration date.[5]

[5] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

2. The presentation of the vehicle should be in the same font size as the official title. Please revise to include "in 5% Dextrose Injection" to be the same font size as "Norepinephrine Bitartrate" to prevent confusion.
3. The presentation of the strength on the carton and container labels and labeling is not consistent with the dosing described in the PI. To reduce the risk for confusion, we recommend revising the strengths for consistency (i.e. 4 mg/250 mL (16 mcg/mL)).

4. The presentation of the storage temperature and temperature excursions noted in section 16 of the PI are not consistent with that seen on the carton and container labels. Consider revising the statement to say: 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].

B. Container Label
   1. Revise [redacted (b) (4)]" to "For Intravenous Infusion Only" to prevent confusion.
   2. We recommend removing [redacted (b) (4)] as this is duplicative. "Single Dose Only" is already present on the labels and labeling.

C. Carton Labeling
   1. Consider revising the statement "Protect from light [redacted (b) (4)]" to read: "Protect from light. [redacted (b) (4)] Keep in overwrap until ready to use."
   2. 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.

[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 MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Norepinephrine Bitartrate in 5% Dextrose Injection received on March 16, 2020 and July 2, 2020 from Baxter Healthcare Corporation, and the listed drug (LD).

Table 2. Relevant Product Information for Norepinephrine Bitartrate in 5% Dextrose Injection and the Listed Drug

Product Name	Norepinephrine Bitartrate in 5% Dextrose Injection, (b) (4)	Levophed (Hospira Inc): NDA 007513
Initial Approval Date	N/A	July 13, 1950
Active Ingredient	Norepinephrine bitartrate	Norepinephrine Bitartrate
Indication	• Restoration of blood pressure in acute hypotensive states. (b) (4)	(b) (4)
Route of Administration	Slow continuous intravenous infusion	(b) (4) slow continuous infusion.
Dosage Form	Injection	Injection
Strength	• 4 mg / 250 mL (16 mcg/mL). Ready to use. • 8 mg / 250 mL (32 mcg/mL). Ready to use.	4 mg/4 mL (1 mg/mL) norepinephrine base in single-dose glass vial or ampule.
Dose and Frequency	- Initial dose of 8 mcg to 12 mcg norepinephrine per minute. - Observe response to initial dose and adjust flow rate to maintain low normal blood pressure	Initial dose of 0.25 mL to 0.375 mL (from 8 mcg to 12 mcg of base) per minute. Adjust the rate of flow to establish and maintain a low to normal blood pressure (usually 80 mm Hg to 100 mm Hg systolic) sufficient to maintain the circulation of vital organs. •Maintenance dose: 0.0625 mL to 0.125 mL per minute (from 2 mcg to 4 mcg of base)

How Supplied	- Twenty (20) 4 mg/250 mL containers - Twenty (20) 8 mg/250 mL containers	1 box of 10 ampules or 10 vials in a carton
Storage	Store at 20° to (b) (4) °C (68° to 77°F) [See USP Controlled Room Temperature]. (b) (4) PROTECT FROM LIGHT. (b) (4)	(b) (4) Protect from light.
Container Closure	Single-dose, ready-to-use VIAFLO containers in an amber/foil overwrap	Glass vial or ampule

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 30, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, norepinephrine. Our search identified no previous reviews for norepinephrine injection.

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 in 5% Dextrose Injection labels and labeling submitted by Baxter Healthcare Corporation.

- Container label received on March 16, 2020
- Carton labeling received on March 16, 2020
- Prescribing Information (Image not shown) received on March 16 2020 and July 2, 2020, available from \\cdsesub1\evsprod\nda214313\0008\m1\us\pi-draft-labeling-text-original-draft-v4-c.docx

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

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