CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214313Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 214313
Norepinephrine Bitartrate in 5% Dextrose Injection
Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Norepinephrine Bitartrate in 5% Dextrose Injection
Strength	4 mg / 250mL and 8 mg / 250mL
Route of Administration	Parenteral (IV infusion)
Rx/OTC Dispensed	Rx
Applicant	(b) (4)
Submissions (s) Reviewed	NDA 214313, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Zhengfu Wang	ONDP/DNDAPI/NDB3
Drug Product/Environmental Assessment (EA)	Akm Khairuzzaman	ONDP/DNDPIII/NDPB5
Process and Facility	Steven Hertz	OPMA/DPMAIV/PMB10
Biopharmaceutics	Nadia Ahmed	ONDP/DB/BB3
Microbiology	Dustin Thomas	OPMA/DMAII/MAB4
RBPM	Grafton Adams	OPRO/ DRBPMI
Application Technical Lead (ATL)	Akm Khairuzzaman	ONDP/DNDPIII/NDPB5

Quality Review Data Sheet

DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE OF REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)		Adequate	12/05/2018	LOA Jan-29-2020
028437	Type III	Baxter	Viaflo Container Closure System	Adequate	8/13/2020	Based on information provided in NDA

Other Documents: *Pre-IND # 138572 meeting minutes for Norepinephrine Bitartrate in 5% Dextrose Injection*

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 214313 (Norepinephrine Bitartrate in 5% Dextrose Injection) is recommended for approval. An expiration period of 7 months is granted for the product when stored at 20°C - 25°C (68°F - 77°F) in the commercial packaging. Product excursions are permitted to 15-30°C (59-86°F).

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Background, and Quality Assessment Summary

The applicant, (b) (4), has sought U.S. marketing approval for Norepinephrine Bitartrate in 5% Dextrose Injection, 4 mg/250mL and 8 mg/250mL for intravenous infusion in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Norepinephrine is a sympathomimetic catecholamine that is indicated for blood pressure control in certain acute hypotensive states. (b) (4). The proposed Norepinephrine Bitartrate in 5% Dextrose Injection is supplied as a ready-to-use, sterile solution in single-dose 250 ml infusion bag. This NDA for Norepinephrine Bitartrate in 5% Dextrose Injection relies for approval, in part, on the FDA's findings of efficacy and safety for the Listed Drug (LD), Levophed 4mg/4ml (NDA 007513). The listed drug product is a concentrate in a vial that requires dilution with 5% dextrose in an infusion bag prior to use. The proposed infusion rate is 8 mcg to 12 mcg norepinephrine per minute (followed by a maintenance dose of 2-4 micrograms per minute). The Listed Drug Product also has the same infusion rate after reconstitution. The scientific bridge between the LD and the proposed drug product was established as per the 21 CFR 320.24(b)(6) through comparisons of formulation and physiochemical data, demonstrating that the differences will not impact the in vivo performance of the proposed drug product. From a quality perspective, the proposed control strategies are adequate to ensure consistent product quality regarding identity, strength, purity, sterility, potency, and stability. Note that the drug product is sensitive to temperature and pH. Stability studies revealed that the batches were close to failing at the end of the proposed (b) (4)-month shelf life and that a statistical approach was requested to ensure that a more commercially robust formulation was approved. This is to avoid future potential recalls and storages. The proposed 7-month shelf life is based on their statistical analysis and found to be acceptable. The out of pouch in use stability data indicated that the product is stable for 30 days. All listed manufacturing facilities are in acceptable condition to commercially manufacture this drug product.

A. Drug Substance (Norepinephrine) Quality Summary

Norepinephrine bitartrate is a compendial (USP & Ph. Eur.) drug substance that exist as norepinephrine bitartrate monohydrate. It is a chiral compound with one chiral center in norepinephrine base and the isomer of R-configuration is used in the drug product. All CMC

information, including structural characterization, impurities, physicochemical properties, manufacturing, specification, batch analysis and stability data have been cross-referenced to DMF (b) (4), held by (b) (4). The DMF (b) (4) has been reviewed in support of this NDA and found adequate. The drug substance is controlled for its identity using three methods namely FTIR, reaction with ferric chloride, reaction with iodine and thiosulfate. It is also controlled for its assay, enantiomeric impurity (D-norepinephrine) and the impurities that are process related and/or degradation products, including residual solvents. Other attributes that are tested at release include appearance, optical rotation, residue on ignition, water determination, (b) (4) content, bacterial endotoxins and microbial bioburden. The analytical procedures used to perform the testing conform (for the most part) to the analytical procedures in the recently established USP Monograph for norepinephrine bitartrate. The combined data provide adequate information about API identification, purity and impurity. The proposed drug substance specification is adequate. The drug substance is stored in (b) (4). The expiration date of (b) (4) has been established.

B.1. Product Design, and Release Specification:

Norepinephrine Bitartrate in 5% Dextrose Injection is a ready-to-use parenteral infusion solution intended for the use as a sympathomimetic catecholamine in patients for blood pressure control. Each mL contains the equivalent of 16 or 32 micrograms base of norepinephrine supplied as 31.90 or 63.80 micrograms per ml of norepinephrine bitartrate monohydrate and the following inactive ingredients: 50 mg/ml dextrose monohydrate (b) (4) water for injection, q.s to 1 mL and sodium hydroxide/ hydrochloric acid for pH adjustment. The recommended clinical dose and infusion rate for the proposed Norepinephrine Bitartrate in 5% Dextrose Injection is identical to the LD. Nitrogen (NF) is used (b) (4) All proposed excipients are compendial grade. No novel or human/animal origin excipients were proposed. All the inactive ingredients are below the levels provided in Inactive Ingredients Database (IID) maintained by FDA. Critical material attributes of the excipients employed in the formulation are controlled as per the relevant USP/NF monographs. The material attributes of the excipients do not directly impact the quality attributes of the finished product. Product release specification, involving testing of product critical quality attributes such as identity, assay for L-norepinephrine, enantiomeric impurity (D-norepinephrine), related substance, (b) (4) pH, osmolality, particulate matter, sterility, elemental impurities (per USP <232>/ICH Q3D requirements), and bacterial endotoxins, is adequate. The analytical procedures have been adequately validated.

B.2. Manufacturing: The manufacturing process utilizes a (b) (4) sterilization. The process steps (b) (4). The process description adequately describes how the controlled parameters for each unit operation and the measured process attributes will produce consistent intermediates of defined properties to make the desired final product. The validated process for (b) (4) sterilization, and container closure integrity testing are adequate. Compatibility of the product with the proposed manufacturing components, i.e., (b) (4) has been

evaluated to define maximum hold time (i.e. (b) (4)) during product manufacturing. The applicant has demonstrated that the drug product batches can be manufactured with consistent quality and purity. Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

B.3. Microbiological Aspects: The manufacturing of the drug product is adequately controlled for microbiological attributes at various stages of the process. (b) (4) The drug product is tested for sterility and is controlled for endotoxins against an acceptable limit of NMT (b) (4) EU/mL and NMT (b) (4) EU/mL for lower and higher strength, respectively. The in-use hold time of 30 days after opening from the overwrap is supported by the microbiological data.

B.4. Biopharmaceutics Aspects: The proposed to-be-marketed drug product, Norepinephrine Bitartrate in 5% Dextrose Injection is not quantitatively and qualitatively the same as the Levophed 4mg/4ml (NDA 007513). The Listed Drug is a concentrate in a vial and requires dilution with 5% dextrose prior to use, whereas the test product is a ready to use intravenous infusion. The recommended clinical dose and rate of infusion for the proposed Norepinephrine Bitartrate in 5% Dextrose Injection is identical to the LD. There is no bioequivalence study. To establish the scientific bridge to the LD as per the 21 CFR 320.24(b)(6), data from comparative *in vitro* physicochemical characteristics (e.g. pH, osmolality, specific gravity, and viscosity), have been provided. The totality of data and information provided, support that the formulation differences between the LD and the proposed drug product are not expected to demonstrate differences in the *in vivo* drug performance. Therefore, a scientific "bridge" between the proposed drug product and the LD has been established to support the 505(b)(2) application and the reliance on FDA's determination of safety and efficacy of the LD. In summary, biopharmaceutics information provided is adequate.

B.5. Container Closure System: The drug product is packaged in a 250 ml Viaflo container closure system (i.e. an infusion bag). The infusion bag is not co-packaged with the catheter, needle and the infusion rate controller. Based on study of leachables and extractables, and pharmaceutical development studies, the applicant has demonstrated compatibility with the active ingredient, excipients, container and closure components, and dosing components. The product stability data also indicate suitability of the proposed container closure system for the intended use.
The applicant has demonstrated the container closure package integrity of Norepinephrine Bitartrate in 5% Dextrose Injection. USP physicochemical [<661>] and biological testing [<87>, <88>, <661.2>] are appropriately performed. Based on the toxicological safety assessment of the available chemical and biological data, negligible risk of adverse effects in humans would be expected under the proposed conditions of manufacturing and storage and clinical use with the Viaflo container

B.6. Product Stability, Expiration Date & Storage Conditions. The applicant provided data from stability studies from three registration batches stored in the intended commercial packaging under long-term conditions (25°C ± 2°C/40% RH ± 5% RH) for up to 12 months, intermediate condition (30°C ± 2°C/35% RH ± 5% RH) for up to 12 months, and accelerated conditions (40°C ± 2°C/25%

RH ± 5% RH) for 6 months. Data reveal that the drug product is sensitive to temperature and pH with respect to isomerization to D-isomer (enantiomeric impurity). There is a downward trending in assay over time at all stability storage condition. Based on the applicant's statistical analysis on the data using the 95% one-sided confidence, the predicted storage time at 25°C for L-norepinephrine to reach a 90% specification is 7.4 months. The stability data and statistical analysis support an expiration dating period of 7 months for the drug product stored in the proposed container closure system at 20 – 25ºC (68 – 77ºF). The product excursions to 15 – 30ºC (59 – 86ºF) are acceptable. Photostability of the proposed product has been demonstrated. Study of product stability under temperature cycling conditions does not show any significant change with respect to all evaluated parameters. The out of pouch in use stability data indicated that the product is stable for 30 days.

C. Assessment of Manufacturing Facilities: The office of Process and Facilities has recommended overall approval for all the currently listed manufacturing facilities concerning this NDA.

D. The applicant has claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) on the basis that no extraordinary circumstances exists under 21 CFR 25.15(d) that would warrant preparation of an environmental assessment. The applicant's claim of categorical exclusion is acceptable.

E. OPQ's all labeling recommendations are reflected in the most recent version of the product labeling

F. Life Cycle Knowledge Information: The drug product is very sensitive to minor changes in pH and temperature. Any future manufacturing changes with respect to these two critical attributes should be considered as a prior approval change. Additionally, note that this product has a stability issue and is approved with 7-month shelf life only because at 9-month time point under the leg-term condition, one batch from each strength exhibited 89% assay. Therefore, any prior approval supplement (PAS) regarding extension of expiry date need be carefully reviewed.

OVERALL ASSESSMENT AND SIGNATURES

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 214313 (Norepinephrine Bitartrate in 5% Dextrose Injection) is recommended for approval.

Akm Khairuzzaman, Ph.D.
Application Technical Lead (ATL)
ONDP/DNDPIII/NDPB5

Akm Khairuzzaman -S

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Life Cycle Knowledge Management

NDA 211215 (Norepinephrine Bitartrate in 5% Dextrose Injection)

Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H (High)**	(b) (4)	Acceptable	Given that the product sterility is the high-risk attribute, any proposed changes in (b) (4) or microbiological testing-related product specification may need to be carefully evaluated.
Bacterial Endotoxin	Formulation Container Closure Process Parameters Scale/equipment/ Site	**H (High)**		Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels will need to be evaluated based on the maximum total daily dose.
Norepinephrine Assay	Temperature and pH	M (Medium)		Acceptable	Any change on sterilization process and pH of the formulation will need to be carefully evaluated
Enantiomeric Purity	pH and Temperature	**M (Moderate)**		Acceptable	Any change on sterilization process and pH of the formulation will need to be carefully evaluated

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QUALITY ASSESSMENT

Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evaluation	Comments
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low)	(b) (4)	Acceptable	
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	**M** **(Moderate)**		Acceptable	(b) (4) directly impacts the level of enantiomeric impurity.
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	**M** **(Moderate)**		Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)		Acceptable	

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Items	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	NOREPINEPHRINE BITARTRATE IN 5% DEXTROSE INJECTION	Acceptable
Established name(s)	NOREPINEPHRINE BITARTRATE IN 5% DEXTROSE INJECTION	Acceptable
Route(s) of administration	IV infusion	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single dose.	Acceptable
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4)	Acceptable
Available dosage form(s)	IV injection	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Follows approved USP product for the LD	Acceptable

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single patient- use). Other package type terms include pharmacy bulk package and imaging bulk package.		

1.2.3 Section 11 (DESCRIPTION)

Items	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	NOREPINEPHRINE BITARTRATE IN 5% DEXTROSE INJECTION	Acceptable
Dosage form(s) and route(s) of administration	IV injection, IV route	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Follows approved USP product for the LD	Acceptable
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided	Acceptable
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	FDA recommended to use equivalence statement of "31.90 or 63.80 micrograms per ml of norepinephrine bitartrate monohydrate" and mention about "50 mg/ml" of dextrose on the labeling	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	Acceptable
Statement of being sterile (if applicable)	Yes	Acceptable
Pharmacological/ therapeutic class	Yes	Acceptable
Chemical name, structural	Yes	Acceptable

formula, molecular weight		
If radioactive, statement of important nuclear characteristics.	Not Applicable	Acceptable
Other important chemical or physical properties (such as pKa or pH)	pH 3.5 – 3.9	Acceptable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity	None present	Acceptable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Items	**Information Provided in the NDA**	**Assessor's Comments**
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	IV Injection	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
Available units (e.g., bottles of 100 tablets)	Twenty (20) 4 mg/250 mL containers Twenty (20) 8 mg/250 mL containers	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient use). Other package terms include pharmacy bulk package and imaging bulk package.	Single dose	Acceptable
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in	Protect from light. (b) (4) (b) (4) the bag can be stored at	Acceptable

original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	room temperature for up to 30 days.	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature [20° to 25°C (68° to 77°F)], excursions permitted to 15° to 30°C (59° to 86°F)	Acceptable
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex free."	Not Applicable	Acceptable
Include information about child-resistant packaging	Not Acceptable	Acceptable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Items	Information Provided in the NDA	Assessor's Comments
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: Baxter Healthcare Corporation Deerfield, IL 60015 USA Made in Ireland	Acceptable

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Not applicable

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Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	Norepinephrine Bitartrate in 5% Dextrose Injection	Acceptable
Dosage strength	4 mg / 250mL and 8 mg / 250mL	Acceptable
Route of administration	Intravenous Infusion	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Follows approved USP product for the LD	Acceptable
Net contents (e.g. tablet count)	250 ml per infusion bag	Acceptable
"Rx only" displayed on the principal display	yes	Acceptable
NDC number	yes	Acceptable
Lot number and expiration date	yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature [20° to 25°C (68° to 77°F)]	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use)	Single dose	Acceptable
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Not applicable	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Acceptable	Acceptable
Name of manufacturer/distributor	Manufactured by:	Acceptable

	Baxter Healthcare Corporation Deerfield, IL 60015 USA Made in Ireland	
Medication Guide (if applicable)	Not Applicable	Acceptable
No text on Ferrule and Cap Overseal	Not Applicable	Acceptable
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Follows approved USP product for the LD.	Acceptable

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

1. In the dosage form and strength section of the package insert, FDA recommended to use "single dose container"
2. In section 3 of the package insert, FDA suggested to change "5% dextrose (b) (4)" to "5% dextrose"
3. FDA suggested to remove the brand name of the container "VIAFLO"
4. In the description section of the package insert, FDA recommended to use equivalence statement of "31.90 or 63.80 micrograms per ml of norepinephrine bitartrate monohydrate" and mention about "50 mg/ml" of dextrose on the labeling
5. The container and over pouch label should be change as follows: (b) (4)" to "Dextrose Monohydrate"

Overall Assessment and Recommendation: **Adequate after the above deficiencies are fulfilled.**

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 8/19/2020.
Secondary Assessor Name and Date (and Secondary Summary, as needed): David Claffey, Ph.D., 8/19/2020.

Akm Khairuzzaman

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David Claffey

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	214313
Drug Product Name/ Strength	Norepinephrine Bitartrate in 5% Dextrose Injection (0.016 mg/mL and 0.032 mg/mL)
Route of Administration	Intravenous
Applicant Name	Baxter Healthcare Corporation
Therapeutic Classification/ OND Division	CDER/ODEI/DCRP
RLD/RS Number	NDA 007513 (Levophed from Hospira)
Proposed Indication	Restoration of blood pressure in acute hypotensive states; (b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: The Applicant, Baxter Healthcare Corporation, has submitted NDA 214313 for the marketing approval of pre-mixed norepinephrine solutions in single-dose VIAFLO containers, available in concentration of 4 mg/250 mL and 8 mg/250 mL, indicated for blood pressure control in certain acute hypotensive states (b) (4) The Listed Drug, Levophed, approved under NDA 007513 on 07/13/1950, requires dilution with 5% dextrose prior to use. The Applicant has not provided any in-vivo bioequivalence studies. Instead, the Applicant is proposing to establish a bridge under 21 CFR 320.24(b)(6) between the Listed Drug and the proposed drug product through comparisons of formulation and physiochemical data, demonstrating that the differences will not impact the in vivo performance of the proposed drug product. The Applicant has demonstrated comparable pH, osmolality, specific gravity, and viscosity characteristics between the proposed drug product and the LD. There are minor differences observed with respect to surface tension that are not expected to impact the proposed drug product's in vivo performance. Additionally, the Applicant has provided supporting assay, related compound impurity, and enantiomeric impurity comparative data. The totality of data and information provided support that the formulation differences between the LD and the proposed drug product are not expected to demonstrate differences in the in vivo drug performance. From a biopharmaceutics perspective, bridging has been established between the proposed drug product and the Listed Drug.

List of Submissions being assessed (table):

Document(s) Assessed	Date Received
NDA 214313	**03/16/20**

Background:

Hospira's Levophed (Norepinephrine Bitrtate Injection, USP) 1 mg/mL (4 mg/4 mL) is a first-line vasopressor indicated for blood pressure control in certain acute hypotensive states (b) (4) Levophed, approved as NDA 007513 on 07/13/1950, is administered by intravenous (IV) infusion. Levophed requires dilution, prior to use, to several different concentrations in clinical practice. The Applicant, Baxter Healthcare Corporation, for this NDA 214313, has proposed pre-mixed norepinephrine solutions in single-dose 250 mL VIAFLO containers, available in concentrations of 4 mg/250 mL (or 0.016 mg/mL) and 8 mg/250 mL (or 0.032 mg/mL). The Applicant has proposed these concentrations since they are the most commonly used concentrations in clinical practice per several healthcare professional's recommendations.[1] Pre-mixed solutions are one way to prevent medication errors and their associated complications. Additionally, these concentrated solutions may be necessary in patients who can not tolerate large volume administration.

Submission:

The Applicant has not provided any in-vivo bioequivalence studies. Instead, the Applicant is proposing to establish a bridge under 21 CFR 320.24(b)(6) between the Listed Drug and the proposed drug product through comparisons of formulation and physiochemical data, demonstrating that the differences will not contribute to the in vivo performance of the drug product.

A formulation comparison is presented in Table 1. Additional comparisons between the active and inactive ingredients, diluent used, and final drug product concentrations can be found in the Summary of Clinical Pharmacology Studies. Differences between the proposed product and the LD include the concentration of active ingredient, diluents, pH adjusters, and the presence of antioxidant. The Listed Drug has a concentration of 1 mg/mL whereas the proposed product has concentrations of 0.016 mg/mL and 0.032 mg/mL. The Applicant cites literature indicating that norepinephrine exhibits linear pharmacokinetics and notes that clinical use requires titration based on individual patient response.

The Listed Drug is available at a concentration of 1 mg/mL in sodium chloride solution, and then further diluted in 5% dextrose (b) (4) or 5% dextrose and

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sodium chloride before administration whereas the proposed product is a premixed IV solution (diluted with 5% dextrose monohydrate). The Average Dosage of the Listed Drug provides a possible dilution of 4 mL (4 mg) of Levophed in 1000 mL of 5% dextrose, for a final concentration of 4 mcg/mL. It is noted that several different concentrations could be prepared, depending on the clinical requirements of each individual patient. The Applicant states that (b) (4) The Listed drug also uses sodium metabisulfite as an antioxidant whereas the proposed drug product does not have any antioxidant in its formulation. Finally, the proposed drug product uses hydrochloric acid and sodium hydroxide in its formulation as pH adjusters, but the Listed Drug does not include these excipients.

The Applicant has summarized formulation differences between the Listed Drug product and the proposed drug product in Table 2. As demonstrated in Table 3, although the concentrations between the proposed drug product and the listed drug product are different, by adjusting infusion rates, the dosage per minute delivered to the patient is the same between the two drug products.

Table 1: Comparison of Ingredients in Proposed Drug Product Compared to Listed Drug

	Baxter Proposed Norepinephrine Bitartrate in 5% Dextrose Injection	Hospira Levophed RLD Norepinephrine Bitartrate Injection USP
Active Ingredient(s)	Norepinephrine (Norepinephrine Bitartrate)	Norepinephrine (Norepinephrine Bitartrate)
Inactive Ingredient(s)		
Dextrose Monohydrate	5% Dextrose, (b) (4) (50 mg/mL)	N/A
Sodium Chloride	N/A	Unknown Quantity
Sodium Metabisulfite	N/A	Vial: not more than 0.2 mg/mL Ampule: not more than 2 mg/mL
Sodium Hydroxide	As Required	N/A
Hydrochloric acid	As Required	N/A
(b) (4)		
Nitrogen	As Required	Unknown
Dosage Form	Injectable	Injectable
Route of Administration	Injection	Injection
Diluent	Premixed with 5% dextrose	Per Levophed Prescribing Information: Levophed should be diluted in 5% dextrose injection or 5% dextrose and sodium chloride injections. These dextrose containing fluids are protection against significant loss of potency due to oxidation.
Strength(s)	4 mg/250 mL and 8 mg/250 mL 0.016 mg/mL and 0.032 mg/mL (16 µg/mL and 32 µg/mL)	4 mg/4 mL (1 mg/mL)

Table 2: Formulation Comparison of Proposed Drug Product to LD[2]

Component	Baxter Proposed Product: Norepinephrine Bitartrate in 5% Dextrose Injection	Reference Product: Levophed (Norepinephrine Bitartrate Injection, USP)
Norepinephrine Bitartrate	0.016 mg/mL and 0.032 mg/mL	1 mg/mL
Dextrose Monohydrate, USP	50 mg/mL	N/A*
Sodium Chloride	N/A	(b) (4)
Sodium Metabisulfite	N/A	0.2 mg/mL
Hydrochloric acid	pH adjustment	N/A
Sodium hydroxide	pH adjustment	N/A
(b) (4)		

N/A= Not Applicable

* Although the LD does not contain dextrose, the Prescribing Information requires further dilution of the contents of the concentrated solution in dextrose containing solutions and provides instructions for dilution in 1 L of 5% dextrose.

Table 3: Sample Doses with Corresponding Infusion Rates for Varying Concentrations of Norepinephrine

Dose (µg/min)	Product and Infusion Rate					
	USPI Dilution Concentration (4 µg/mL)		Baxter 4 mg/250 mL (16 µg/mL)		Baxter 8 mg/250 mL (32 µg/mL)	
	mL per minute	mL per hour	mL per minute	mL per hour	mL per minute	mL per hour
8	2	120	0.5	30	0.25	15
12	3	180	0.75	45	0.375	22.5
2	0.5	30	0.125	7.5	0.0625	3.75
4	1	60	0.25	15	0.125	7.5

B.12 BRIDGING OF FORMULATIONS

Assessment: *{Adequate}*

The Applicant has conducted comparative physicochemical tests with the pre-mixed proposed drug product in comparision with the diluted Listed Drug product. The pH and osmolality data on diluted Levophed (Listed Drug) and Norepinephrine Bitartrate in 5% Dextrose Injection are comparable, indicating the absence of an impact on physicochemical characteristics of the proposed product due to qualititative (buffer components hydrochloric acid and sodium hydroxide, sodium metabisulfite, sodium chloride) and quantitative ((b) (4) agents sodium chloride and dextrose monohydrate) differences with respect to

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formulation. It is noted that the LD includes an antioxidant, sodium metabisulfite, that the proposed drug product does not include.

The Applicant has provided data demonstrating that the differences in formulation do not impact product quality and are not expected to cause differences in in-vivo performance. The average pH of the proposed drug product is 3.8 whereas the average pH of the LD is 4.0. The data show comparable pH values between the proposed drug product and the LD. discipline. The two drug products have enantiomeric purity specifications, also to be evaluated by the drug product review discipline.

In summary, the Applicant demonstrated comparable pH, osmolality, specific gravity, and viscosity characteristics between the proposed drug product and the LD. The minor differences observed with respect to surfact tension is not expected to impact product's performance. The Applicant has also provided supporting assay, related compound impurity, and enantiomeric impurity comparative data. The totality of data and information provided support that the formulation differences between the LD and the proposed drug product are not expected to demonstrate differences in the in vivo drug performance. From a biopharmaceutics perspective, bridging is established between the proposed product and the LD. For reference, bridging information and data are included in: Formulation Bridging Studies (page 61 - 80).

B. R. REGIONAL INFORMATION

Comparability Protocols

Assessment: *{Adequate/Inadequate}*
None

Post-Approval Commitments

Assessment: *{Adequate/Inadequate}*
None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date: Nadia Lisa Ahmed, 07/14/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed): Poonam Delvadia, 07/14/2020

Nadia Ahmed

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Poonam Delvadia

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CHAPTER VII: MICROBIOLOGY
IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214313
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Norepinephrine Bitartrate in 5% Dextrose Injection (4 mg/250 mL and 8 mg/250 mL)
Route of Administration	Intravenous
Applicant Name	Baxter Healthcare Corporation
Therapeutic Classification/ OND Division	CDER/OND/ODEI/DCRP
Manufacturing Site	Baxter Healthcare S.A Moneen Road Castlebar, County Mayo, Ireland F23 XR63
Method of Sterilization	(b) (4) Sterilization

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
NDA 214313 0000 (1)	**03/16/2020**
0003 (4)	**05/20/2020**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The submission is in the eCTD format; some figures and tables have been copied from the original application. The amendment dated 05/20/2020 is in response to an IR sent 05/13/2020.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents:
- D243787MR02R01.doc dated 04/03/2018 (inadequate) and D24378MR02R02.doc dated 11/21/2018 (adequate) for CCIT validation
- D24378M06R01.docx dated 09/30/2019 (adequate) for 250 mL Viaflo CCIT validation, environmental monitoring
- D24378M08R01.docx (adequate) for (b) (4) sterilizer validation

S Drug Substance

Drug substance is non-sterile and not reviewed – N/A

P.1 Description of the Composition of the Drug Product

Description of drug product – Clear, colorless to light yellow sterile solution for intravenous injection only.

Drug product composition –

Ingredient	Function	4 mg/250 mL		8 mg/250 mL	
		Quantity per mL	Quantity per unit	Quantity per mL	Quantity per unit
Norepinephrine, USP	API	0.016 mg	4 mg	0.032 mg	8 mg
Dextrose Monhydrate, USP/Ph. Eur.	(b) (4)	50 mg	12.5 g	50 mg	12.5 g
Sodium Hydroxide NF/Ph. Eur.	pH Adjuster	As required	As required	As required	As required
Hydrochloric Acid, NF/Ph. Eur.	pH Adjuster	As required	As required	As required	As required
Water for Injection, USP/Ph. Eur.	Vehicle	QS	QS	QS	QS
Nitrogen, Ph. Eur.	(b) (4)	N/A	N/A	N/A	N/A

(b) (4)

Assessment: ***Adequate***

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

(b) (4)

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Jesse Wells

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Dustin Thomas

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/s/

AKM KHAIRUZZAMAN
08/20/2020 08:39:43 AM
Recommended for Approval from Quality Perspective