CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215700Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215700		
Applicant Name	InfoRLife SA		
Drug Product Name	Norepinephrine Bitartrate in Sodium Chloride Injection		
Dosage Form.	Injection		
Proposed Strength(s)	4 mg per 250 mL (16 mcg per mL), 8 mg per 250 mL (32 mcg per mL), 16 mg per 250 mL (64 mcg per mL)		
Route of Administration	Intravenous		
Maximum Daily Dose	See clinical review.		
Rx/OTC Dispensed	Rx		
Proposed Indication	Restoration of blood pressure in adult patients with acute hypotensive states.		
Drug Product Description	Norepinephrine in 0.9% sodium chloride is a clear, colorless premixed 250 mL solution filled in 300 mL Nexcel® bags with a tube port and a twist-off port. Each bag is packed in a sealed overwrap with an oxygen scavenger and oxygen indicator.		
Co-packaged product information	N/A		
Device information:	This product is a combination product, and the bag (primary container) includes tube and twist-off ports.		
Storage Temperature/ Conditions	20°C to 25°C. Protect from light. Do not freeze.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Ben Zhang ONDP/DNDAPI/NDB3	Zhengfu Wang ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Akm Khairuzzaman ONDP/DNDPIII/NDPB5	Theodore Carver ONDP/DNDPIII/NDPB5
	Manufacturing	Upasana Sahu OPMA/DPMAIV/PMB12	Sateesh Sathigari OPMA/DPMAIV/PMB12

	Biopharmaceutics	Zhuojun Zhao OPQ/ONDP/DB/BB3	Kimberly Raines OPQ/ONDP/DB/BB3
	Microbiology	Jianli Xue OPMA/DMAI/MAB2	Nandini Bhattacharya OPMA/DMAI/MAB2
	Other (specify):	N/A	
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 24 months is granted for the drug product stored at 20°C to 25°C (68°F to 77°F) in the original carton to protect from light.

b. Additional Comments for Action: None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Conclusion:
The Office of Pharmaceutical Quality Review team has assessed NDA 215700 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports the drug product to have. As such, OPQ recommends approval of this NDA from a quality perspective.

2.) Background:
The Applicant, InfoRLife SA., submitted NDA 215700 on November 19, 2021. The Applicant seeks approval in this 505(b)(2) NDA for Norepinephrine Bitartrate in Sodium Chloride Injection, 4 mg/250 mL (0.016 mg/mL), 8

mg/250 mL (0.032 mg/mL) and 16 mg/250 mL (0.064 mg/mL) for intravenous (IV) administration. The listed drug product for this application is Hospira's LEVOPHED® (Norepinephrine Bitartrate) injection, EQ 4 mg base/4mL, approved under NDA 007513.

3.) Summary of critical aspects of the drug product design:

The drug product contains norepinephrine bitartrate, sodium chloride USP, and water for injection USP, with hydrochloric acid and sodium hydroxide added as needed to adjust pH. The drug product is designed to be ready for use for continuous infusion without further dilution, as a 250 mL solution in 300 mL Nexcel® bags. The listed drug, which is a concentrated norepinephrine solution, is intended to be diluted prior to use, contains sodium metabisulfite as an antioxidant, and the labeling for the listed drug indicates that it must be diluted in dextrose-containing solutions to inhibit oxidation. The proposed drug product in this NDA does not contain any antioxidants or other ingredients that retard oxidation, such as dextrose, and therefore, the risk of oxidation for the proposed norepinephrine formulation is significant. This risk has been mitigated by packaging the drug product immediate container (plastic bag) in a plastic/foil overwrap that contains an oxygen scavenger and oxygen indicator, which is supported by development and manufacturing studies that support proper functioning of each product component. Long-term stability data confirm that the drug product is stable through the proposed shelf life of 24 months. In addition, the drug product in the Nexcel® bag was confirmed to be stable, including stability to oxidation and photodegradation, for a period of up to seven days of removal from the overwrap based on in-use stability data. Therefore, the risk of oxidation and photodegradation of the commercial drug product has been adequately mitigated when it is stored and administered according to the instructions in its labeling.

4.) Other aspects of the quality review:

The supporting quality information provided for the drug substance, manufacturing, and microbiology reviews were found to be adequate after the Applicant addressed issues raised during review. All facilities were approved based on previous inspection history. The biopharmaceutics review concluded that the scientific bridge between the proposed and listed drug products is adequately supported by physicochemical comparison of the proposed drug product to the listed drug as diluted prior to administration. There are no outstanding deficiencies for any of the OPQ review disciplines.

5.) Quality labeling: The quality labeling review identified two deficiencies that needed to be corrected, the incorrect pH range listed for the drug product in the prescribing information, and a lack of specification of the color change in the overwrap labeling. These deficiencies have been addressed by the Applicant and therefore, the revised quality labeling is adequate.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Choose an item.
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

The drug product is very sensitive to changes in pH, temperature and light. Any future manufacturing changes that may affect these critical attributes should be considered as a prior approval change. In addition, the container/closure system includes critical components (oxygen indicator and absorber) that prevent oxidation and photodegradation of the drug product. Based on these aspects of the drug product and its stability, proposals to extend the expiration dating should be carefully reviewed.

Theodore Carver

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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	None	Acceptable
Established name(s)	NOREPINEPHRINE BITARTRATE IN SODIUM CHLORIDE 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)	Unacceptable. Should read as follows (section 3): 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)
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	Single dose.	Acceptable

package and imaging bulk package.		
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)	Section 2.1 of the PI instructs to check for discoloration prior to administration. Overwrap labeling instructs not to use the product if the oxygen indicator changes its color.	Unacceptable None of this instruction specify what color is considered as unacceptable.
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	Equivalence statement should be next to strengths. See dosage form and strength above.
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.	Single dose	Acceptable

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 SODIUM CHLORIDE 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.	Provided under section 11 of the labeling as follows: *"Each mL contains the equivalent of 16, 32 or 64 micrograms of norepinephrine base supplied as 32, 64 or 128 micrograms per mL of norepinephrine bitartrate monohydrate. It contains sodium chloride (9 mg/mL) and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment"*	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 formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	Not Applicable	Acceptable
Other important chemical or physical properties (such as pKa or pH)	Section 11 says, *"It has a pH of* (b) (4) *."*	Unacceptable: Labeling needs to be edited reflecting the recent change in pH acceptable range: 3.4-4.0 in the drug product specification.
Remove statements that may be misleading or promotional (e.g.,	None present	Acceptable

"synthesized and developed by Drug Company X," "structurally unique molecular entity		

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)	Not applicable	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 original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store in original carton (b) (4) to protect from light. (b) (4)	Acceptable
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)], (b) (4) (b) (4)	Acceptable
Latex: If product does not contain latex and manufacturing of product	Not Applicable	Acceptable

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."		
Include information about child-resistant packaging	Not Acceptable	Acceptable

1.2.6 Manufacturing Information After Section 17 (for drug products)

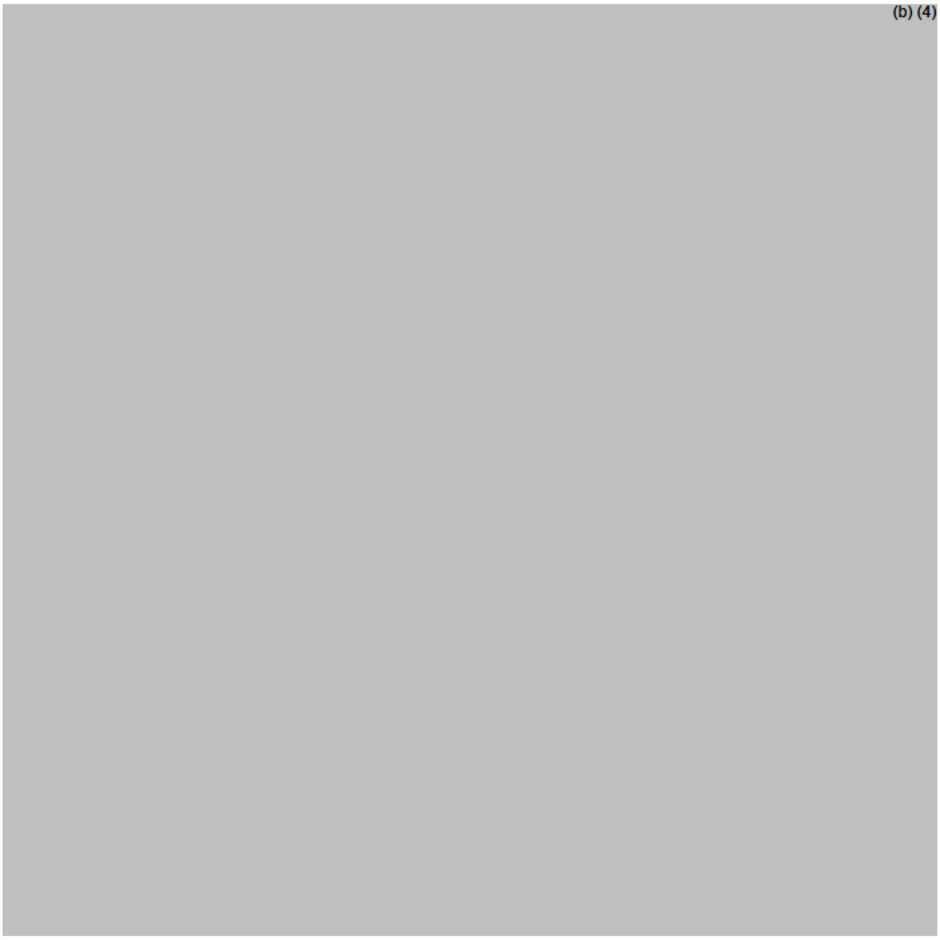
Items	**Information Provided in the NDA**	**Assessor's Comments**
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: WG Critical Care, LLC Paramus, NJ 07652 Made in Switzerland	Acceptable

2.0 PATIENT LABELING

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

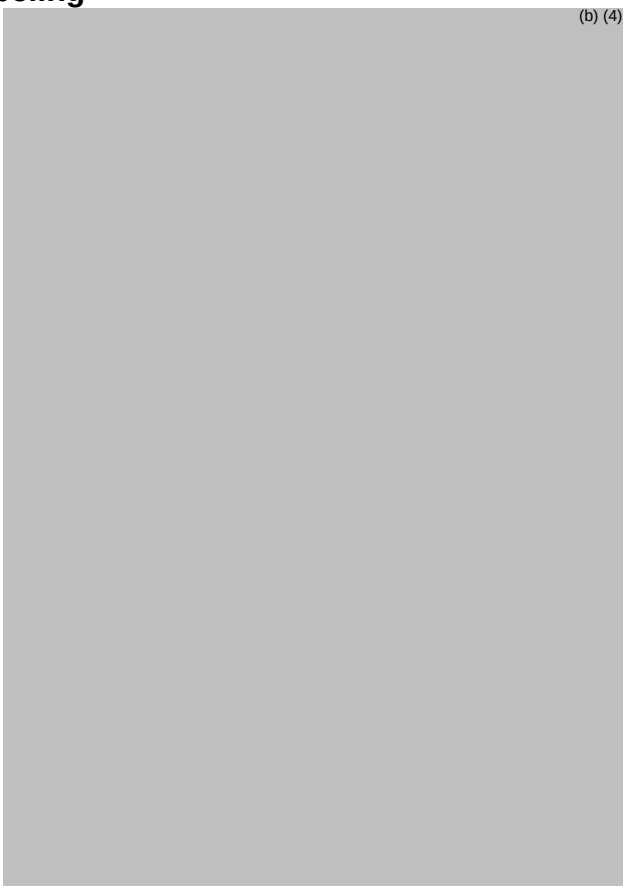
3.0 CARTON AND CONTAINER LABELING

3.1 Container Label (infusion bag label)



Note: The two other lower strengths have identical information except for strength, NDC number & box color to differentiate strengths (green for 4 mg/250 ml & blue for 8 mg/250 ml)

3.2 Overwrap Labeling



Note: The two other lower strengths have identical information except for strength, NDC number & box color to differentiate strengths (green for 4 mg/250 ml & blue for 8 mg/250 ml)

3.3 Carton Labeling

Note: The two other lower strengths have identical information except for strength, NDC number & box color to differentiate strengths (green for 4 mg/250 ml & blue for 8 mg/250 ml)

Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	Norepinephrine Bitartrate in 0.9% Sodium Chloride Injection	Acceptable
Dosage strength	4 mg / 250mL, 8 mg / 250mL, and 16 mg/250 mL	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	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 for: WG Critical Care, LLC Paramus, NJ 07652 Made in Switzerland	Acceptable

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: Inadequate

1. *pH range do not match the revised product specification*
2. *The overwrap instructs not to use if the oxygen indicator change the color. However, it does not specify what color is indicated to discard the product.*

ITEMS FOR ADDITIONAL ASSESSMENT

1. Revise the dosage form and strength of the PI to read:
"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)"

2. Revise the pH on the container closure and labeling to match the recently revised specification.
3. The overwrap labeling instructs not to use the product if the oxygen indicator changes its color. Specify the color in such instruction.

Overall Assessment and Recommendation: *Package insert, Carton and Container Labeling comment should be sent out to the Applicant.*

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 3/2/2022.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Theodore Carver, Ph.D., 4/25/2022

Theodore Carver

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Akm Khairuzzaman

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	215700
Assessment Cycle Number	001
Drug Product Name/ Strength	Norepinephrine Bitartrate in Sodium Chloride Injection, 4 mg/250 mL (0.016 mg/mL), 8 mg/250 mL (0.032 mg/mL) and 16 mg/250 mL (0.064 mg/mL)
Route of Administration	Intravenous infusion
Applicant Name	InfoRLife SA
Therapeutic Classification/ OND Division	Division of Cardiology and Nephrology (DCN)
List Drug (LD) Number	007513
Proposed Indication	To raise blood pressure in adult patients with severe, acute hypotension

Assessment Recommendation: **Adequate**

Assessment Summary:

This 505(b)(2) Application seeks approval for Norepinephrine Bitartrate in Sodium Chloride Injection, 4 mg/250 mL (0.016 mg/mL), 8 mg/250 mL (0.032 mg/mL) and 16 mg/250 mL (0.064 mg/mL) for intravenous (IV) administration, which is indicated to raise blood pressure in adult patients with severe, acute hypotension. The Listed Drug (LD) is Hospira's LEVOPHED® (Norepinephrine Bitartrate) injection, EQ 4 mg base/4 mL, approved under NDA 007513.

This Biopharmaceutics Assessment evaluated the overall data supporting the bridge between the proposed drug product and the LD product.

InfoRLife SA's proposed Norepinephrine Bitartrate in Sodium Chloride Injection is a formulated solution intended for the same indications and has the same active ingredient, dosage form, dose, dosing regimen, and route of administration as the LD product, but is different in concentration and excipients. Due to the difference, a biowaiver under *21 CFR 320.22(b)(1)* is not feasible. However, a bridge between the proposed drug product and the LD product can be established based on *21 CFR 320.24 (b)(6)*.

The difference in API concentration, difference of sodium chloride and dextrose at the point of patient contact as well as the absence of Sodium Metabisulfite in the proposed Norepinephrine Bitartrate in Sodium Chloride Injection is found unlikely to affect the in vivo disposition of Norepinephrine in human. The Applicant also provided comparative physicochemical data, which showed comparable pH and osmolality between the proposed and the LD products.

Therefore, the Applicant has provided sufficient information to support the bridge between the proposed Norepinephrine Bitartrate in Sodium Chloride Injection and the listed drug, LEVOPHED® (Norepinephrine Bitartrate) injection under *21CFR 320.24 (b) (6)*.

List Submissions Being Assessed:

Documents Assessed	Date Received
0001 (1) Original Submission	November 19, 2021
0004 (4) Response to IR	January 26, 2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: None

B.1 DRUG SUBSTANCE

The drug substance is Norepinephrine Bitartrate USP, same as the API in the LD product LEVOPHED® (Norepinephrine Bitartrate) injection. The Applicant found that Norepinephrine Bitartrate is freely soluble in water (1 in 2.5).

B.2 DRUG PRODUCT

The composition of the proposed Norepinephrine Bitartrate in Sodium Chloride Injection is shown in Table 1.

Table 1: Norepinephrine Bitartrate in Sodium Chloride Injection, 4 mg/250 mL (0.016 mg/mL), 8 mg/250 mL (0.032 mg/mL) and 16 mg/250 mL (0.064 mg/mL)

Norepinephrine Bitartrate in Sodium Chloride injection,					
Active Substance(s)	**Quantity mg/mL**	**Quantity mg/mL**	**Quantity mg/mL**	**Function**	**Reference to standard**
Norepinephrine Base (as Norepinephrine Bitartrate)	0.016 0.032	0.032 0.064	0.064 0.128	API	USP
Excipient(s)					
Sodium Chloride	9	9	9	(b) (4)	USP
Hydrochloric acid	q.s to pH	q.s to pH	q.s to pH	pH adjuster	NF
Sodium Hydroxide	q.s to pH	q.s to pH	q.s to pH	pH adjuster	NF
Water for injection	q.s to 1 mL	q.s to 1 mL	q.s to 1 mL	Solvent	USP

B.2 BRIDGING OF FORMULATIONS

InfoRLife SA's proposed Norepinephrine Bitartrate in Sodium Chloride Injection is provided as a (b) (4) solution, available in three concentrations (4 mg/250 mL, 8 mg/250 mL and 16 mg/250 mL), while the LD LEVOPHED® (Norepinephrine Bitartrate) injection, 4 mg/4 mL need to be diluted to a suitable concentration for infusion.

The following information is evaluated in support of the bridging between the proposed drug product and the LD product:

1. Formulation, dosage form, and administered volume
2. Comparative physicochemical data

1) Formulation, dosage form and administered volume

The Applicant provided the comparative quantitative composition between the proposed Norepinephrine Bitartrate in Sodium Chloride Injection and LEVOPHED® before and after dilution are shown in **Table 2** and Table **3**, respectively.

Table 2: Comparative Compositions of LEVOPHED® Before Dilution and InfoRLife's Proposed (b) (4) Drug Product

Composition: Norepinephrine Bitartrate in Sodium Chloride Injection			
	RLD (undiluted)	InfoRlife	
Components:	Quantity (per mL):		Function
Active Substance: - Norepinephrine Base	1 mg	0.016 mg/mL 0.032 mg/mL 0.064 mg/mL	Active ingredient
- (as Norepinephrine Bitartrate)	1.89 mg	0.032 mg/mL 0.064 mg/mL 0.128 mg/mL	
Sodium chloride, USP	yes	9 mg	(b) (4)
Sodium Metabisulfite, USP	0.2 mg	/	Antioxidant
Sodium hydroxide or Hydrochloric Acid	/	q.s to pH	pH adjuster
Water for Injection	1 mL	1 mL	Solvent

Table 3: Comparative Compositions of LEVOPHED® After Dilution and InfoRLife's Proposed (b) (4) Drug Product

Ingredients	LEVOPHED® (µg/mL)[1]				InfoRLife's Proposed Drug Product (µg/mL)		
Strength	1000				16	32	64
Norepinephrine Base	1000	16	32	64	16	32	64
Sodium Metabisulfite	200	3.2	6.4	12.8	-	-	-
Sodium Chloride	(b) (4)				9000	9000	9000
A) If diluted with 5% Dextrose Injection							
Dextrose	-	49200	48400	46800	-		
Total Sodium Chloride	-	(b) (4)					
B) If diluted with 5% Dextrose and 0.9% Sodium Chloride Injection							
Dextrose	-	49200	48400	46800			
Total Sodium Chloride	-	(b) (4)					

Assessment: *{Adequate}*

[1] \\CDSESUB1\evsprod\nda007513\0043\m3\32-body-data\32p-drug-prod\norepinephrine-bitartrate-injection-01\32p1-desc-comp\description-and-composition.pdf

Based on the proposed label, InfoRLife's Norepinephrine Bitartrate in Sodium Chloride Injection is a ready to use intravenous injection solution, whereas LEVOPHED® is presented as a concentrated solution (4 mg/4 mL) to be diluted with 5% dextrose or sodium chloride injection solution with 5% dextrose to a final concentration of 4 mcg/mL prior to administration. Higher concentration solutions might be used in patients requiring fluid restriction per LEVOPHED® label. Based on the flexibility in preparation of the final concentration for intravenous infusion, the proposed concentrations 16, 32 and 64 mcg/mL of INFORLIFE's Norepinephrine Bitartrate in Sodium Chloride Injection is deemed acceptable from Biopharmaceutics perspective.

The difference in amount of sodium chloride and Dextrose at the point of patient contact from INFORLIFE's Norepinephrine Bitartrate in Sodium Chloride Injection and the diluted LD product is unlikely to affect the in vivo disposition of Norepinephrine.

Also, sodium Metabisulfite is used as preservative (antioxidant) in the LD product. The absence of Sodium Metabisulfite in InfoRLife's Norepinephrine Bitartrate in Sodium Chloride Injection is not expected to affect the in vivo disposition of Norepinephrine.

2) Comparative Physicochemical Data

In IR response dated January 26, 2022, the Applicant provide physicochemical analysis with three different production lots of the LD product LEVOPHED® 4 mg/4 mL vial (**Table 4**) diluted to 0.064 mg/mL using diluents, 5% Dextrose Injection. The measured data were done in triplicate and mean values were reported and compared to the proposed Norepinephrine Bitartrate in Sodium Chloride Injection, 0.064 mg/mL (**Table 5**).

Table 4: Details of the LD Product LEVOPHED® 4 mg/4 mL vial (Undiluted)

	RLD Levophed Batch 27385BD	RLD Levophed Batch 041103A	RLD Levophed Batch 750503A
Clarity	Clear	Clear	Clear
Color	-	-	-
pH (pH units)	3.5	3.5	3.4
Osmolality (mOsmol/kg)	271	272	272
Analysis Date	January 19, 2022	January 19, 2022	January 19, 2022
Expiry Date[1]	September 2022	October 2020	September 2018

Table 5: Comparison between Applicant Product and RLD (diluted to 0.064 mg/mL in 5% Dextrose)

	RLD Levophed Batch 27385BD diluted	RLD Levophed Batch 041103A diluted	RLD Levophed Batch 750503A diluted	8R011 Norepinephrine 0.064 mg/mL	8R012 Norepinephrine 0.064 mg/mL	8R013 Norepinephrine 0.064 mg/mL
Clarity	Clear (< 3 NTU)	Clear (< 3 NTU)	Clear (< 3 NTU)	Clear (< 3 NTU)	Clear (< 3 NTU)	Clear (< 3 NTU)
Color	< Y6	< Y6	< Y6	< Y6	< Y6	< Y6
pH (pH units)	4.0	4.0	4.0	3.7	3.6	3.6
Osmolality (mOsmol/kg)	268	268	267	290	290	290
Analysis Date	January 19, 2022	January 19, 2022	January 19, 2022	June 22, 2020	June 22, 2020	June 22, 2020
Expiry Date	September 2022	October 2020	September 2018	June 2020	June 2020	June 2020

The Applicant used two expired LEVOPHED® batches for the analysis, and states that this does not have an impact on the comparison since the physicochemical properties are the same of the batch not at expiry. Also, the Applicant only tested one concentration, i.e., 0.064 mg/mL, as the Applicant considers the API does not have an impact on physicochemical characteristics due to the low concentration of Norepinephrine in the Drug product.

Assessment: ***{Adequate}***

As shown in Table 5, INFORLIFE's proposed Norepinephrine Bitartrate in Sodium Chloride Injection, 0.064 mg/mL has similar pH (3.6-3.7) and osmolality (290 mOsmol/Kg) comparable to those of the diluted LD product, LEVOPHED® at 0.064 mg/mL (pH 4.0, osmolality 267-268 mOsmol/kg). In addition, INFORLIFE's proposed Norepinephrine Bitartrate in Sodium Chloride Injection, 0.016 and 0.032 mg/mL shown in Table 6 have similar pH and Osmolality to the LEVOPHED® at 0.064 mg/mL in Table 5 as well as at 0.016 and 0.032 mg/mL reported in other Applications[2].

Table 6: Physicochemical Property Data for the Proposed Norepinephrine Bitartrate in Sodium Chloride Injection[3]

Strength	0.016 mg/mL			0.032mg/mL			0.064 mg/mL		
Lot #	8R005	8R006	8R007	8R008	8R009	8R010	8R011	8R012	8R013
pH	3.7	3.6	3.7	3.7	3.6	3.7	3.7	3.6	3.6
Osmolality (mOsmol/kg)	281	285	284	285	282	284	284	287	284

Primary Biopharmaceutics Assessor's Name and Date: Zhuojun Joan Zhao, Ph.D., June 28, 2022

Secondary Assessor Name and Date: Kimberly Raines, Ph.D., July 1, 2022

[2] https://panorama fda.gov/task/view?ID=5f904ee80002b9216796675118b7f8bb and https://panorama.fda.gov/task/view?ID=611ff81300a0ee67a82323ec4ec22231

[3] \\CDSESUB1\evsprod\NDA215700\0001\m3\32-body-data\32p-drug-prod\norepinephrine-bitartrate-in-sod-chloride-i-injectable-inforlife\32p5-contr-drug-prod\32p54-batch-analys

Zhuojun Zhao

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Kimberly Raines

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215700
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Norepinephrine Bitartrate in Sodium Chloride Injection / 4 mg/250 ml, 8 mg/250 ml, 16 mg/250 ml
Route of Administration	Injection
Applicant Name	InfoRLife SA
Therapeutic Classification/ OND Division	CDER/OND/OCHEN/DCN
Manufacturing Site	InfoRLife SA CH-7748, Campascio Switzerland
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original submission	11/19/2021
IR response	1/26/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: None

Concise Description of Outstanding Issues: None

Supporting Documents: Microbiology review N (b) (4) MR01.doc (adequate) dated 9/7/2018 for information regarding (b) (4) (b) (4); A (b) (4) MR01.doc (adequate) dated 4/30/2021for information regarding (b) (4).

S DRUG SUBSTANCE

Assessment: ***Adequate***

The drug substance is not procured sterile. The API [redacted] manufacturing facility. Therefore, microbiology review will not be conducted for drug substance.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Sterile solution supplied in 300 ml Nexcel bag equipped with two tubing ports and one twist off port.

- **Drug product composition –**

Table 1: Norepinephrine Bitartrate in Sodium Chloride Injection, 0.016 mg/mL, 0.032 mg/mL and 0.064 mg/mL

Norepinephrine Bitartrate in Sodium Chloride injection,					
Active Substance(s)	**Quantity mg/mL**	**Quantity mg/mL**	**Quantity mg/mL**	**Function**	**Reference to standard**
Norepinephrine Base (as Norepinephrine Bitartrate)	0.016 0.032	0.032 0.064	0.064 0.128	API	USP
Excipient(s)					
Sodium Chloride	9	9	9	[redacted]	USP
Hydrochloric acid	q.s to pH	q.s to pH	q.s to pH	pH adjuster	NF
Sodium Hydroxide	q.s to pH	q.s to pH	q.s to pH	pH adjuster	NF
Water for injection	q.s to 1 mL	q.s to 1 mL	q.s to 1 mL	Solvent	USP

- **Description of container closure system –** The drug product is filled in 300 ml Nexcel bag equipped with two tubes and a twist off port (supplier: [redacted]). [redacted]. The twist off port is used for administration.

[redacted]

Each filled bag is packed in [redacted]/aluminum/[redacted] overwrap and oxygen scavenger and oxygen indicator is placed inside the overwrap.

Exhibit batches # 8R005, 8R006, 8R007 (4 mg/250 ml); 8R008, 8R009, 8R010 (8 mg/250 ml); 8R011, 8R012, 8R013 (16 mg/250 ml): [redacted] L, [redacted] bags
Proposed commercial batch: [redacted] L, [redacted] bags (manufactured using [redacted]); [redacted] L, [redacted] bags (manufactured using [redacted])

Assessment: ***Adequate***

The sponsor provided an adequate description of the drug product's composition and container closure system.

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Jianli Xue

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Nandini Bhattacharya

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Theodore Carver

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