CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215700Orig1s000

NON-CLINICAL REVIEW(S)

Memorandum

Division of Pharmacology/Toxicology
Office of Cardiology, Hematology, Endocrinology, & Nephrology
Center for Drug Evaluation and Research

Date: April 20, 2022

Application: NDA 215700-Sequence 0007

From: Rama Dwivedi
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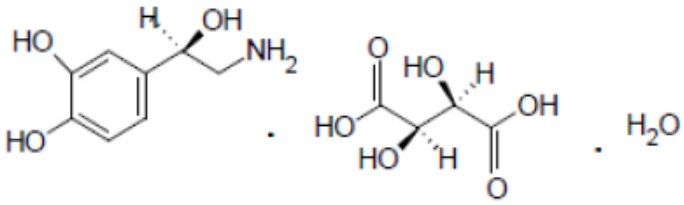
Drug Product: Norepinephrine Bitartrate in Sodium Chloride Injection, 4 mg/250 mL (0.016 mg/mL), 8 mg/250 mL (0.032 mg/mL) and 16 mg/250 mL (0.064 mg/mL)

Chemical Name: − (-)-α-(Aminomethyl)-3,4-dihydroxybenzyl alcohol tartrate (1:1) (salt), monohydrate (USP)

CAS number: 108341-18-0

Molecular Formula: $C_8H_{11}NO_3.C_4H_6O_6.H_2O$

Structural Formula:



Molecular weight: 337.3

Indication: [redacted] (b) (4)

Subject: Permitted Daily Exposure (PDE) determination for the Safety assessment of the leachable analytes identified in Norepinephrine Bitartrate Drug Product.

Applicant: InfoRlife

Background Information

InfoRlife submitted NDA 215700 for the approval of a Norepinephrine single-dose [redacted] (b) (4) with a concentration of 4 mg/250 mL (0.016 mg/mL), 8 mg/250 mL (0.032 mg/mL), 16 mg/250 mL (0.064 mg/mL) under the 505(b)(2) pathway, packaged in 250 mL plastic Nexcel® infusion bags, with aluminum overwrap. The reference listed drug (RLD) NDA 007513 (Norepinephrine Bitartrate in Sodium Chloride Injection, as a concentrated solution of 1 mg/mL) was submitted by Hospira and

approved on July 13, 1950. It is marketed in United States under the name of Levophed ®. The active ingredient, route of administration, dosage form of the proposed drug product is the same as that of the Reference Listed Drug (NDA 007513). The proposed drug product, Norepinephrine Bitartrate in Sodium Chloride Injection, is a ready-to-use injectable solution that does not require further dilution.

Norepinephrine Bitartrate Injection in InfoRlife's drug product is filled into IV bags (Nexcel® (b) (4) material) with two connector tubes made from (b) (4), and bags are overwrapped using (b) (4)/Aluminum/(b) (4) flexible overwraps with oxygen absorber and oxygen indicator. The details of the Container and Closure system is below.

Container Closure System	Component	Raw Material Supplier	Supplier	DMF number
Non PVC-latex free bags	(b) (4)			
Connector Tubing				
Port: Twist off port				

Each filled bag is packed in (b) (4) / Aluminum / (b) (4) overwrap, Oxygen scavenger and Oxygen indicator.

Component	Material	USP compliance
Bag	(b) (4)	Component tested in accordance with tests, methods, and acceptance criteria listed in USP <661.1> Material of construction, as for (b) (4) statement
Tube		Information not available
		USP <661> Physicochemical Tests – Plastics
Twist off		Component tested in accordance with tests, methods, and acceptance criteria listed in USP <661.1> for the material (b) (4)
		Component tested in accordance with tests, methods, and acceptance criteria listed in USP <661.1> for the material (b) (4).

There are two means of demonstrating that a material of construction has met the requirements of 661.1. The first means is to perform the testing contained within 661.1 and meet the specifications in 661.1. The second means is the use of a material in the packaging system of a currently approved finished drug product. Specifically, 661.1 states "Individual plastic materials of construction are considered to be well characterized if they meet the requirements in this chapter or are used in a packaging system that meets the requirements in Plastic Packaging Systems for Pharmaceutical Use" (USP 661.1)

Materials from IV bags (Nexcel® (b) (4) material) have potential to come in direct or indirect contact with the drug product releasing leachable lysates and trigger an adverse toxic effect. To identify and qualify such leachable analytes in Norepinephrine Bitartrate for Injection in IV-bags (Nexcel® (b) (4)

material), an extractable/leachable study was conducted (Protocol N° UR038-01- February 25, 2022) by [redacted] (Nexcel® supplier) to calculate and determine the total daily dose of each leachable compound and to compare with the safety concern threshold (SCT) or its Permitted Daily Exposure (PDE) to support the safety qualification. To have the acceptable Permitted Daily Exposure (PDE) of leachable compounds above the SCT from IV-bags, a Nonclinical IR was submitted (as below) to Sponsor on February 24, 2022, for all leachable analytes identified:

"This is in reference to your UR038 Risk Assessment of E/L in norepinephrine bitartrate injection in Nexcel [redacted] container closure system submitted under 3.2.P.7 of NDA-215700. We do not agree with your approach to calculate the RI as the justification for the maximum daily intake of the identified analytes, as per referenced article (Jenke and Carlson, 2014) which extensively uses the LD50 data. We recommend that you recalculate the PDEs for all leachable analytes above the AET (Except: [redacted]), based on the modifying factors described in ICH Q3C and Q3D (F1, F2, F3, F4, F5, and F6) for toxicological evaluations. Please also note that we accept the SCT at [redacted] µg/day which can be used to calculate the AET; however, we do not accept reliance on Cramer classification for toxicology evaluation."

To demonstrate the quality and safety of the drug product, InfoRlife, submitted the data obtained from the E/L Study (Protocol N° UR038-01- conducted on February 25, 2022) to calculate the total daily intake of each leachable compound in norepinephrine bitartrate injection packaged in proposed IV-bags ([redacted] container closure system). The present review is to determine a). if the submitted *PDEs* by the sponsor of the leachable analytes that are above the SCT in Norepinephrine Bitartrate for Injection IV-film bag material ([redacted]), are acceptable from the pharmacology and toxicology's perspective, and b) if the TDI of each leachable compound (that is above the SCT) is shown to be below the PDE, with a safety margin.

Safety Evaluation of Extractable/Leachable (E/L) analytes in Norepinephrine Bitartrate for Injection in IV-bag system (Nexcel® [redacted] material) Container Closure System (CCS)

The extractable study (Protocol N° UR038-01 dated February 25, 2022) was performed by the Nexcel® supplier using multiple solvent and experimental conditions to identify and quantify leachable compounds in Norepinephrine Bitartrate for Injection to establish the quality and safety of drug product packaged in proposed IV bags ([redacted] container closure system). The extract was analyzed for the compounds that leach from the material into solution as below.

Extraction medium

The solvent used for extractable is acidified water pH 3, alkaline water pH 11.0 and 50% ethyl alcohol in water.

Following extraction, the chemical tests below are performed

- LC/UV for Non- volatile residue (NVR);
- GC/MS for Semi-volatile and volatile residue;
- ICP/MS for inorganic elements.

Extraction stoichiometry

The sample to be test was completely immersed in the extraction solvent using a solvent ratio of 6 cm^2/mL.

Extraction techniques

Solvent soaking
Sample keep at 50°C for 72 hours

Reporting threshold

Volatile Compound: [redacted] µg/L
Semi volatile Compound: [redacted] µg/mL
Non volatile Compound [redacted] µg/mL

Sample extracts were subjected to following analytical techniques for the detection, identification and (estimated) (semi-)quantification of compounds of different physicochemical properties (the sensitivity and adequacy of these assays are under the CMC purview and therefore it is deferred to their review):

1. Headspace Gas Chromatography / Mass Spectrometry (HS-GC/MS) screening to determine Volatile Organic Compounds (VOC)
2. Gas Chromatography / Mass Spectrometry (GC/MS) screening to determine Semi-Volatile Organic Compounds (SVOC)
3. High Resolution Accurate Mass (HRAM) Ultra Performance Liquid Chromatography / Mass Spectrometry (UPLC/MS APCI) screening to determine Non-Volatile Organic Compounds (NVOC)
4. Inductively Coupled Plasma / Mass Spectrometry (ICP/MS) for mercury analysis
5. Ion Chromatography (IC) for anions

Analytical evaluation threshold (AET) was calculated based on the ICH M7 guideline on mutagenic impurities for parenteral applications (safety concern threshold-SCT of = (b) (4) µg/day. The AET for the (b) (4) is based on the threshold level of (b) (4) compounds, i.e., (b) (4) µg/day. This is considered acceptable.

Safety concern threshold (PQRI)	(b) (4) µg/day
Maximum daily administered volume to the patient	365 mL
Approximate surface area	435 cm^2
Drug product volume/bag	250 mL
Maximum daily bag surface area exposed to the patient (=435 cm^2 * 0.365 L / 0.25 L)	0.06 m^2
Analytical Evaluation Threshold (AET) in drug product (µg/L) (b) (4) µg/day / 0.365 L/day)	(b) (4) µg/L
Analytical Evaluation Threshold (AET) expressed in function of bag surface area (µg/m^2) (b) (4) µg/day / 0.06 m^2/day)	(b) (4) **µg/m^2**
Analytical Evaluation Threshold (AET) in extract* ((b) (4) µg/L) * 250mL / 81mL	(b) (4) **µg/L**

**Results in µg/L are obtained on extract of 6 cm^2/mL (250 mL bags filled with 81mL)*

Norepinephrine is indicated for (b) (4) patients are exposed to the drug and potential extractables for a short period of time (hours/day). Data from E/L study was analyzed and evaluated for toxicological risk assessment for the leachable lysates present in Norepinephrine Bitartrate for Injection in IV-bag system (Nexcel® (b) (4) material). PDE calculation was performed as per ICH Q3C guidance. All leachables found at levels below or equal to (b) (4) µg/day do not need to be assessed, as its level is considered to be so low that it presents negligible safety concerns from carcinogenic and non-carcinogenic toxic effects.

Leachable analytes with TDI of > (b) (4) µg/day were evaluated for mutagenic potential using the published literature review. Evaluation also included consideration of sensitization and irritation potential. If a leachable was not a mutagen or a sensitizer, the SCT of (b) (4) µg per day for general toxicity can be applied. Although we generally recommend the use of NMT (b) (4) µg/day as the qualification threshold to account for general toxicities and sensitizers, but the sponsor's evaluation included consideration for sensitization and irritation, and it is therefore considered acceptable to use a SCT of (b) (4) µg per day for general toxicities. For sensitizer and irritants, a SCT of (b) (4) µg per day is used. The PDEs were calculated as additional safety threshold. To account for differences in absorption and bioavailability via different administration routes, an additional bioavailability adjustment factor, Factor 6, is applied to calculate the PDE. If no information on bioavailability is available, a default factor of 10 is proposed for oral to parenteral extrapolation for small organic compounds.

PDE = NOAEL x Weight Adjustment/F1 x F2 x F3 x F4 x F5 x F6.

The modifying factors adopted are the following:

F1 = 5 to account for the extrapolation from rat to humans.

F2 = 10 to account for differences between individuals (humans).

F3 = 5 as the duration of the study is 3 months.

F4 = 1 no severe toxicity is anticipated.

F5 = 1 as the no effect level was determined.

F6 = 10 as the absorption after oral administration in not established

Oral Bioavailability	Bioavailability Adjustment Factor (F6)
< 1 %	Divide by 100
≥1 to < 50	Divide by 10
≥ 50 to < 90%	Divide by 2
≥ 90%	Divide by 1

Compound	CAS	Structure	TDI	PDE	Evaluation
(b) (4)					No safety concern

Compound	CAS	Structure	TDI	PDE	Evaluation
(b) (4)					No safety concern

Compound	CAS	Structure	TDI	PDE	Evaluation
[redacted]				(b) (4)	No safety concern

Compound	CAS	Structure	TDI	PDE	Evaluation
[redacted]				(b) (4)	No safety concern

Compound	CAS	Structure	TDI	PDE	Evaluation
[redacted]				(b) (4)	No safety concern

Compound	CAS	Structure	TDI	PDE	Evaluation
[redacted]				(b) (4)	No safety concern

Compound	CAS	Structure	TDI	PDE	Evaluation
[redacted]				(b) (4)	No safety concern

Compound	CAS	Structure	TDI	PDE	Conclusion
(b) (4)					No safety concern
					No safety concern

Compound	CAS	Structure	TDI	PDE	Conclusion
(b) (4)					No safety concern

Compound	CAS	Structure	TDI	PDE	Conclusion
(b) (4)					No safety concern

Results of *in vitro* bacterial and mammalian gene/tox studies (Ames, mammalian mutagenicity and chromosomal aberration) did not demonstrate any mutagenic or clastogenic effects of any leachable compounds identified in the E/L studies conducted by the Sponsor.

Recommendation

The Permitted daily exposure (PDE) values calculated by the Sponsor for the leachable analytes identified in norepinephrine bitartrate injection (NDA-215700) container closure system (Nexcel (b) (4)) from the E/L study (Protocol N° UR038-01) are in compliance with ICH Q3C guidance. The tiered risk assessment approach, including the PDE values, support the safety qualification of leachable analytes above the Safety Concern Thresholds. We, therefore, conclude that the proposed PDEs for leachable analytes are acceptable, and the leachable analytes at the level demonstrated are considered qualified from the pharmacology and toxicology's perspective.

References

(b) (4)

(b) (4)

International Council for Harmonization (ICH). ICH harmonized guideline: assessment and control of DNA (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, M7 (R1), current step 4 version: https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf. Published: 31 Mar 2017.Updated: 31 May 2017.

ICHQ6A Specification: test procedures and acceptance criteria for new drug substance and new Drug Product: Chemical substances. ICH Q3B (R2) Impurities in New Drug Product

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/s/

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