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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	212909
Supporting document/s:	SDN-1, -5, -6, -7, -8, -9, and -14
Applicant's letter date:	December 21, 2018, February 28, 2019, March 26, 2018, May 15, 2019, May 23, 2019, June 28, 2019, and September 4, 2019
CDER stamp date:	December 21, 2018, February 28, 2019, March 26, 2018, May 15, 2019, May 23, 2019, June 28, 2019, and September 4, 2019
Product:	Phenylephrine Hydrochloride Injection, USP
Indication:	The treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia
Applicant:	Sintetica SA
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Marcus S. Delatte, PhD
Team Leader:	Newton H. Woo, PhD
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1 Executive Summary

1.1 Introduction

The Applicant is seeking marketing approval for phenylephrine hydrochloride as an injectable intravenous solution for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia. This 505(b)(2) application relies upon the safety and efficacy of Vazculep (phenylephrine hydrochloride, NDA 204300) and relevant pharmacology, pharmacokinetics, and toxicology information in the approved label of the listed drug. There is extensive clinical history with phenylephrine hydrochloride, as there are multiple marketed approved phenylephrine-containing drug products.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were submitted to support the proposed NDA. The Applicant is relying upon the Agency's previous finding of safety and efficacy of Vazculep to support the application. The Applicant did not submit blood compatibility data or local tissue tolerance studies for the drug product formulation. However, the drug product formulation is (b) (4) (b) (4) The risk of local effects or blood compatibility concerns are not expected to be higher than the referenced drug product.

There are no novel excipients in the drug product formulation. All drug substance impurities, drug product degradants, (b) (4) and elemental impurities are within acceptable levels in accordance with ICH guidances. The container closure system, glass ampoules, has been adequately justified for safety with respect to concerns for extractables and leachables.

From a nonclinical perspective, the product labeling should be identical to the referenced product labeling.

Because the referenced drug product has four outstanding postmarketing requirements (PMRs) as of the date of this review, we recommend that PMRs also be issued to this Applicant, unless the PMRs issued to Vazculep are fulfilled prior to the action. The PMRs recommended are as follows:

1. Conduct a fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.
2. Conduct an embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.
3. Conduct an embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.
4. Conduct a peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 212909 may be approved with the recommended labeling and PMRs (if necessary).

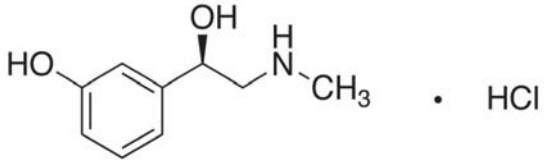
1.3.3 Labeling

From a nonclinical perspective, the nonclinical parts of the drug product label should be identical to the label of the listed drug.

2 Drug Information

2.1 Drug

Table 1. Drug Substance Information

Generic Name	(-)-*m*-hydroxy-α-[(methylamino) methyl] benzyl alcohol hydrochloride
Pharmacological Class	Alpha-1 adrenergic receptor agonist [Established Pharmacological Class]
Structure	
Molecular Formula	$C_9H_{13}NO_2 \cdot HCl$
IUPAC Name	3-[(1R)-1-hydroxy-2-(methylamino)ethyl]phenol, hydrochloride
Molecular Weight	203.67 g/mol
CAS Registry Number	61-76-7

2.2 Relevant INDs, NDAs, BLAs and DMFs

Relevant DMF and NDA applications identified by the PT Reviewer are briefly discussed below in the provided text. Note that the Applicant neither opened nor referenced any IND applications.

Table 2. Relevant DMFs

Application No.	Subject	Holder	DMF Type	Status
[redacted]	[redacted]	[redacted] (b) (4)	II	Active
			III	

(b) (4)		
	III	

Table 3. Relevant NDA Application

Application No.	Sponsor	Product	Indication	Status (Date)
204300	Avadel Legacy Pharmaceuticals, LLC	Vazculep (phenylephrine hydrochloride)	Treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia	Approved (2014)

2.3 Drug Formulation

The drug product is formulated as an injectable solution that is intended for intravenous use. See the table below for excipients included in the drug product. This product is prepared as (b) (4) (0.1 (b) (4) mg/mL). The fill volumes are 5 mL (0.1 mg/mL solution) (b) (4) in glass ampules. (b) (4)

Table 4. Ingredients Employed in the Drug Product (Excerpt from Application)

The following table provides the composition per ml and per ampoule for Phenylephrine 0.1 mg/mL:

Material	Function	Quantity (mg/ml)	Quantity (mg/5 ml)	Unit	Ref.
Phenylephrine HCl	Drug substance	0.100	0.500	mg	USP current ed.
Sodium Chloride	(b) (4)	9.000	(b) (4)	mg	
Hydrochloric Acid (b) (4	(b) (4)		(b) (4)	mg	
Water for injections (b) (4)				mg	
				--	
TOTAL				mg	

(b) (4)

(b) (4)

Maximum Daily Dose: The maximum daily dose for this product is not straight forward. During discussion of the referenced product application, the Division clinical team concluded that based on typical usage patterns, although some rare individuals may be exposed to more than 10 mg, a reasonable maximum recommended daily dose

can be set at <10 mg per 60 kg individual. Of note, the current Applicant based some of their safety evaluations on a maximum daily dose of (b) (4) mg based on a worst-case surgical procedure of 8 hours and the maximum infusion rate of 200 mcg/min (b) (4) . They note that this is a large overestimate of typical surgical procedures and cite two publications that discuss lengthy procedures (Gastmeier et al., 2011; Leong et al., 2006). Although we agree that this would be a worst-case scenario, this drug product is intended to be used periodically through a surgical procedure to treat hypotension and is not likely to be used continuously. Following discussion with the review team, the Division will continue to use <10 mg as an MDD to set impurity and degradant thresholds and will utilize a human daily dose of 10 mg as the reference dose for exposure margins in labeling.

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product.

2.5 Comments on Impurities/Degradants of Concern

The drug substance and drug product specifications for impurities do not exceed ICH qualification thresholds for a drug with a maximum daily dose of <10 mg; therefore, the specifications are acceptable.

Drug Substance

Table 5. Drug Substance Impurity Specifications

Impurity	Proposed Specification (NMT)	ICH Qualification Threshold* (NMT)	Acceptable? (Yes/No)
(b) (4)	(b) (4)	(b) (4)	Yes
(b) (4)			

Drug Product

Table 7. Drug Product Stability Specifications

Test	Proposed Specification (NMT)	ICH Specification/Threshold#	Acceptable? (Yes/No)
(b) (4) Impurity (b) (4)	(b) (4)	(b) (4)	Yes
			Yes
Osmolality		N/A	Yes*; normal serum is (b) (4) mOsm/kg
pH	3.0 to 5.0	N/A	Yes; as per the Applicant, the pH

			(b) (4)

#Maximum Daily Dose set at < 10 mg/day by the Division.
*The proposed osmolality range for this parenteral drug product is acceptable because normal serum osmolality is approximately (b) (4) mOsmol/L and parenteral solutions typically have comparable range. The Applicant has set the same specification for osmolality for both the 0.1 mg/mL (b) (4) solutions.
**The Applicant did not propose a specification for specific individual impurities. Because the ICH Q3B identification threshold is (b) (4) %, this is acceptable.

Container Closure System

The container closure system proposed for use are a 5 mL (0.1 mg/mL solution) (b) (4) glass ampoules (see CMC review for details on the ampoule; also DMFs (b) (4) and (b) (4) As per the CMC review team, extractable/leachable testing is not needed to support the safety of the proposed glass ampoules, which have been used in comparable FDA-approved drug products (see CMC review).

Elemental Impurities

The Applicant evaluated three batches of each (b) (4) drug product (5 mL of 0.1 mg/mL (b) (4) for elemental impurities in accordance with ICH Q3D (They analyzed the product for (b) (4) The only elemental that was detected at levels above the LOQ ((b) (4) ppb) was (b) (4) The maximum (b) (4) level detected in various drug product lots was (b) (4) ppm (see Table below).

(b) (4)

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Phenylephrine is proposed for intravenous administration (bolus or infusion) in patients with clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia. The maximum recommended bolus injection is 200 mcg with a maximum infusion rate of 200 mcg/min. Based on previous discussions with the clinical team the maximum daily dose is not expected to exceed 10 mg per 60 kg individual. For the purposes of this review and for labeling the human daily dose will be 10 mg/day.

2.7 Regulatory Background

There were no meetings or communications between the Agency and Applicant prior to the submission of the NDA.

3 Studies Submitted

The NDA is relying on the Agency's previous findings of safety and efficacy for the Vazculep product; therefore, no new nonclinical studies were submitted to support its approval.

4 Pharmacology

No new pharmacology studies were conducted to support this NDA. A literature search was completed by the Applicant. No new information was identified that would alter the referenced product labeling. The following information on the pharmacology of phenylephrine hydrochloride is from the referenced Vazculep label (Avadel Legacy Pharmaceuticals, LLC, 2014).

12.1 Mechanism of Action

Phenylephrine hydrochloride is an α-1 adrenergic receptor agonist.

12.2 Pharmacodynamics

Interaction of phenylephrine with α1-adrenergic receptors on vascular smooth muscle cells causes activation of the cells and results in vasoconstriction. Following phenylephrine hydrochloride intravenous administration, increases in systolic and diastolic blood pressures, mean arterial blood pressure, and total peripheral vascular resistance are observed. The onset of blood pressure increase following an intravenous bolus phenylephrine hydrochloride administration is rapid, typically within minutes. As blood pressure increases following intravenous administration, vagal activity also increases, resulting in reflex bradycardia. Phenylephrine has activity on most vascular beds, including renal, pulmonary, and splanchnic arteries.

5 Pharmacokinetics/ADME/Toxicokinetics

No new pharmacokinetics/ADME/toxicokinetic studies were completed to support this NDA. A literature search was completed by the Applicant. No new information was identified that would alter the referenced product labeling. The following information on human pharmacokinetic parameters of phenylephrine hydrochloride is from the referenced Vazculep label (Avadel Legacy Pharmaceuticals, LLC, 2014).

12.3 Pharmacokinetics

Following an intravenous infusion of phenylephrine hydrochloride, the observed effective half-life was approximately 5 minutes. The steady-state volume of distribution of approximately 340 L suggests a high distribution into organs and peripheral tissues. The average total serum clearance is approximately 2100 mL/min. The observed phenylephrine plasma terminal elimination half-life was 2.5 hours.

Phenylephrine is metabolized primarily by monoamine oxidase and sulfotransferase. After intravenous administration of radiolabeled phenylephrine, approximately 80% of the total dose was eliminated within first 12 h; and approximately 86% of the total dose was recovered in the urine within 48 h. The excreted unchanged parent drug was 16% of the total dose in the urine at 48 h post intravenous administration. There are two major metabolites, with approximately 57 and 8% of the total dose excreted as *m*-hydroxymandelic acid and sulfate conjugates, respectively. The metabolites are considered not pharmacologically active.

6 General Toxicology

No new general toxicology studies were completed to support this NDA. A literature search was completed by the Applicant. No new information was identified that would alter the referenced product labeling.

7 Genetic Toxicology

No new genetic toxicology studies were completed to support this NDA. A literature search was completed by the Applicant. No new information was identified that would alter the referenced product labeling. The following information on the genetic toxicology of phenylephrine hydrochloride is from the referenced Vazculep label (Avadel Legacy Pharmaceuticals, LLC, 2014).

> *Mutagenesis:* Phenylephrine hydrochloride tested negative in the in vitro bacterial reverse mutation assay (*S.typhimurium* strains TA98, TA100, TA1535 and TA1537), the in vitro chromosomal aberrations assay, the in vitro sister chromatid exchange assay, and the in vivo rat micronucleus assay. Positive results were reported in only one of two replicates of the in vitro mouse lymphoma assay.

8 Carcinogenicity

No new carcinogenicity studies were completed to support this NDA. A literature search was completed by the Applicant. No new information was identified that would alter the referenced product labeling. The following information on the carcinogenicity of phenylephrine hydrochloride is from the referenced Vazculep label (Avadel Legacy Pharmaceuticals, LLC, 2014).

> *Carcinogenesis:* Long-term animal studies that evaluated the carcinogenic potential of orally administered phenylephrine hydrochloride in F344/N rats and $B6C3F_1$ mice were completed by the National Toxicology Program using the dietary route of administration. There was no evidence of carcinogenicity in mice administered approximately 270 mg/kg/day (131-times the maximum recommended daily dose of < 10 mg/day) or rats administered approximately 50 mg/kg/day (48-times the maximum recommended daily dose of < 10 mg/day) based on body surface area comparisons.

9 Reproductive and Developmental Toxicology

No new reproductive and developmental studies were completed to support this NDA. Note that the Sponsor conducted a literature search to identify relevant published studies to use for informing the recommended labeling language. All of the relevant studies submitted for review were previously reviewed to write the approved Vazculep label. The following information on the reproductive and developmental toxicology of phenylephrine hydrochloride is from the referenced Vazculep label (Avadel Legacy Pharmaceuticals, LLC, 2014).

8.1 Pregnancy

(b) (4)

Risk Summary

(b) (4)

Data

Animal Data

(b) (4)

10 Special Toxicology Studies

Local Tolerance

No local tissue toxicity studies or in vitro blood compatibility studies were completed for this product. The Applicant did not identify any nonclinical studies to address this issue.

Because the drug product is formulated (b) (4) and the concentration to be infused is comparable to the referenced drug product, there would appear to be limited new risk for local tissue toxicity compared to the referenced drug product. Given the extensive clinical history of intravenous phenylephrine at comparable concentrations and the nature of the drug product vehicle, the local tissue toxicity of the drug product should be no greater than the referenced drug product. See the clinical review for a discussion of the clinical experience.

11 Integrated Summary and Safety Evaluation

Avadel Legacy Pharmaceuticals' NDA 212909 for phenylephrine hydrochloride, an alpha-1 receptor agonist, was submitted via the 505(b)(2) regulatory pathway with the Vazculep product (NDA 204300) as the referenced product. The clinical history of phenylephrine hydrochloride is extensive. Based on the Agency's previous findings of safety and efficacy of Vazculep (phenylephrine hydrochloride) and its long history of clinical use, repeat-dose toxicology and local tolerance studies evaluating this drug substance are not required for approval of this NDA application. The impurities/degradants/residual solvents/elemental impurities are controlled at acceptable levels in both the drug substance and the drug product. There are no toxicologic concerns when the product is used at levels up to the human daily dose of 10 mg per 60 kg individual. Therefore, NDA 212909 may be approved with labeling comparable to that of the referenced drug product and with PMRs for the full reproductive and developmental toxicology battery if adequate data are not present in the referenced product labeling.

12 Appendix/Attachments

Bibliography

Gastmeier P, Sohr D, Breier A, Behnke M and Geffers C (2011) Prolonged duration of operation: an indicator of complicated surgery or of surgical (mis)management? *Infection* **39**:211-215.

Leong G, Wilson J and Charlett A (2006) Duration of operation as a risk factor for surgical site infection: comparison of English and US data. *J Hosp Infect* **63**:255-262.

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