

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212909Orig1s000

SUMMARY REVIEW



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
 Division of Anesthesia, Analgesia, and Addiction Products
 10903 New Hampshire Ave., Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	October 21, 2019
From	Rigoberto Roca, M.D. Deputy Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Deputy Division Director Summary Review
NDA Number	212909
Applicant Name	Sintetica S.A.
Date of Original Submission	December 21, 2018
PDUFA Goal Date	October 21, 2019
Proprietary Name / Established (USAN) Name	Biorphen (Phenylephrine hydrochloride Injection USP, 0.1 mg/mL) Phenylephrine hydrochloride Injection USP. (b) (4) for Intravenous Administration
Dosage Forms / Strength	0.1 mg/mL (b) (4)
Proposed Indication	Treatment of clinically important hypotension in the setting of anesthesia
Action	Approval (0.1 mg/mL strength)

Material Reviewed/Consulted: OND Action Package, including:	
Pharmacology/Toxicology	Marcus Delatte, PhD; Newton Woo, PhD; Dan Melon, PhD
OPQ/ONDP and OPF	Sukhamaya (Sam) Bain, PHD; Donna F. Christner, PhD; Jizhou Wang, PhD; Julia Pinto, PhD; Derek Smith, PhD; Edwin Jao, PhD; Jason Morgan, PhD; David Bateman, PhD; John Metcalfe, PhD; B. J. Ryan, PhD; Ruth Moore, PhD; Anika Lalmansingh, PhD
ONDP/DB	Kamrun Nahar, PhD; Kelly M. Kitchens, PhD
Clinical Pharmacology Review	Wei Qiu, PhD; Yun Xu, PhD
OPDP	L. Shenee Toombs; Sam Skariah
OSE/DMEPA	Sarah K. Vee, PharmD; Otto L. Townsend, PharmD
DPMH	Carrie Ceresa, PharmD, MPH; Miriam Dinatale, DO; Lynne P. Yao, MD, OND
Project Management Staff	Allison Meyer; Parinda Jani

DB = Division of Biopharmaceutics
 DMEPA = Division of Medication Error Prevention and Analysis
 DPMH = Division of Pediatric and Maternal Health
 OND = Office of New Drugs
 ONDP = Office of New Drug Products

OPF = Office of Process and Facilities
 OPDP = Office of Prescription Drug Promotion
 OPQ = Office of Pharmaceutical Quality
 OSE = Office of Surveillance and Epidemiology

1. Introduction

The Applicant, Sintetica S.A., has submitted a new drug application (NDA) under the 505(b)(2) regulations for two presentations of phenylephrine. The Applicant propose to rely entirely on the Agency's finding of safety and efficacy of NDA 204300 for Vazculep (Phenylephrine Hydrochloride) Injection USP. which was approved on June 27, 2014.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant. This review will also serve as the cross-discipline team leader (CDTL) review.

2. Background

Phenylephrine is a synthetic form derived from epinephrine and has been used clinically for more than 50 years. It is an α 1-adrenergic receptor agonist, with little or no activity on α -2 receptors or β -receptors. The primary site of action is the vascular smooth muscle cells, resulting vascular smooth muscle contraction and subsequent increases in the systolic and diastolic blood pressures. Phenylephrine has also been noted to cause a reflex bradycardia and a decrease in the cardiac output, presumably due to the increased afterload. Phenylephrine has also been demonstrated to have an effect on renal, pulmonary, and splanchnic arteries, but minimal to no effect on cerebral vessels.

Regulatory History

The regulatory history of this application was reviewed by Dr. Bazini and she provided the following summary to be included in this review:

Meeting/Communication/Date	Event/Key clinical issues
September 7, 2018	(b) (4)
October 24, 2018	(b) (4)
December 21, 2018	NDA 212909 submitted and received by DAAAP

Meeting/Communication/Date	Event/Key clinical issues
March 4, 2019	<p>NDA Filed, with multiple review issues identified.</p> <p>Clinical issues included (verbatim from 74-Day Letter):</p> <ol style="list-style-type: none"> 1. Although the proposed label is in the general PLLR format, you must submit data to support this information in your label. Therefore, submit a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, an interim or final report of an ongoing or closed pregnancy registry (if applicable), and a review of the existing nonclinical reproductive and developmental toxicology data. 2. Your communication on January 11, 2019, states that “additional literature reference published after the approval of the VAZCULEP NDA is only intended to support the safety update of our application.” To be consistent with this statement, revise and submit all applicable documents in your NDA application (i.e., clinical overview, clinical summary of efficacy, and integrated summary of efficacy (ISS)) to clearly state that you intend to rely only on the information in the Vazculep label to support efficacy of your product, and remove references to any additional literature that were not utilized to support efficacy in the Vazculep NDA.
May 15, 2019	<p>Applicant submitted SD 7</p> <p>Includes revised ISS and ISE, Summary of Clinical Efficacy, Summary of Clinical Safety, as well as provided literature to support use in pregnant and lactating women. Additional assessment for use in pregnant and lactating women was provided in SD 5 submitted on February 28, 2019.</p>

The Applicant’s submission was [REDACTED] (b) (4) [REDACTED] for the 0.1 mg/mL presentation.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

Drug Substance

With respect to the drug substance, the OPQ review noted the following:

For the drug substance CMC, the applicant has referenced DMF [REDACTED] (b) (4) [REDACTED]

which has been found adequate by the Agency. The NDA includes the applicant's controls of the drug substance, (b) (4)

Based upon the current adequacy of the DMF and upon APPEARS THIS WAY ON ORIGINAL (b) (4)
the information provided in the NDA, the drug substance characterization, shelf-life specification, container closure system and stability are satisfactory.

Drug Product

The following summary description of the drug product is reproduced from the OPQ team's review:

In addition to the API, the drug product contains Water for Injection as the (b) (4) sodium chloride (b) (4) and (b) (4) hydrochloric acid for adjusting pH (b) (4). The (b) (4)

and immediate administration; thus, there is no preservative in the product. The manufacturing process involves (b) (4)

(b) (4) The drug product composition and manufacturing process are satisfactory.

All drug substance and drug product facilities are satisfactory based upon pre-approval inspection as well as history at the Agency's database.

The applicant (b) (4) submitted the NDA for (b) (4) the drug product, 0.1 mg/mL (b) (4). The qualities of the drug product components and of the finished drug product, including characterizations, specifications, test procedures and impurity profiles, have been found adequate. (b) (4)

(b) (4) The (b) (4) 0.1 mg/mL strength is recommended for approval, with an expiration dating of 36 months. (b) (4)

The applicant has requested a biowaiver in accordance with 21 CFR 320.22(b)(1), and provided adequate justification for the differences, in terms of inactive ingredients and physiochemical properties, between the proposed and the listed drug product. Consistent with 21 CFR 320.24 (b)(6), an adequate biobridge has been established between the listed and the proposed drug product. Thus, the NDA is recommended for approval from Biopharmaceutics perspective.

The drug product manufacturing process involves (b) (4). Based upon (b) (4)

bulk solution, ampoule depyrogenation, container closure integrity, and specifications and test results involving Bacterial Endotoxins and Sterility, the drug product has been found adequate from Microbiology perspective.

Facilities Reviews/Inspections

As noted above, all drug substance and drug product facilities are considered to be satisfactory.

Product Quality Microbiology

As noted above. The drug product was found to be satisfactory from a microbiology perspective.

Outstanding or Unresolved Issues

The review team concluded that the Applicant submitted adequate information to support the 0.1 mg/mL presentation. (b) (4)

(b) (4) On September 19, 2019, the Applicant submitted (b) (4) (b) (4) the NDA active for the 0.1

I concur with the review team (b) (4) the 0.1 mg/mL presentation can be approved.

4. Nonclinical Pharmacology/Toxicology

The Applicant did not conduct any nonclinical pharmacology or toxicology studies in support of this NDA, and is relying on the relevant pharmacology, pharmacokinetics, and toxicology information in the approved label for Vazculep.

The following summary is reproduced from Dr. Delatte's review:

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 the drug (b) (4) (b) (4)

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.

Outstanding or Unresolved Issues

I agree with the review team that there are no nonclinical pharmacology/toxicology issues that would preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant did not conduct any clinical pharmacology studies and is relying on the Agency's previous finding of safety and efficacy of Vazculep® (phenylephrine hydrochloride Injection, (b) (4) NDA 204300). The Applicant submitted a request for a biowaiver and provided a justification for the difference in the inactive ingredients, as well as comparative physicochemical properties between the proposed product and the listed product. The request was granted by the biopharmaceutics reviewers.

Drs. Qui and Xu concluded that there was no need for additional clinical pharmacology information.

Outstanding or Unresolved Issues

I agree with the review team that there are no clinical pharmacology issues that would preclude approval of this application.

6. Clinical Microbiology

The drug product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical-Efficacy

The Applicant did not conduct any clinical trials in support of the efficacy of their drug product. Instead, the Applicant is relying on the Agency's finding of efficacy for NDA 204300 for Vazculep (Phenylephrine Hydrochloride) Injection USP.

Outstanding or Unresolved Issues

I agree with the review team that there are no efficacy issues identified that would preclude approval of this application.

8. Safety

The Applicant did not conduct any clinical trials in support of the safety of their drug product. Instead, the Applicant is relying on the Agency's finding of safety NDA 204300 for Vazculep (Phenylephrine Hydrochloride) Injection USP.

The Applicant submitted additional safety information, which was not intended to support the approval of the application, but instead to support the safety update. This consisted of the following:

10 randomized, prospective studies published in literature

- Aragao et. al. 2014 (pregnant patients)
- Das et. al. 2011 (pregnant patients)
- Doherty et. al. 2012 (pregnant patients)
- Gunda et. al. 2010 (pregnant patients)
- Mohta et. al. 2015 (pregnant patients)
- Ngan Kee et. al. 2009 (pregnant patients)
- Ngan Kee et. al. 2013 (pregnant patients)
- Sen et. al. 2013 (pregnant patients)
- Siddik-Sayyid et. al. 2014 (pregnant patients)
- Soeding et. al. 2013 (patients undergoing shoulder surgery)

4 review/retrospective literature studies (all in pregnant patient population)

- Heesen et. al. 2014
- Jeon et. al. 2014
- Strouch et. al. 2015
- Veesser et. al. 2012

Safety information from Applicant's post-marketing database

The Applicant's product Biorphen has been marketed in Europe since April, 2016.

(b) (4)

The Applicant's product Phenylephrin has been marketed in Switzerland since March, 2017.

(b) (4)

Sponsor submitted postmarketing data after European approvals:

- 1 Individual Case Study Report has been received from the EU market (lack of effect)
- No deaths neither any serious adverse event reported
- 5 total case reports identified (1 spontaneous report and 4 from literature)
 - 4/5 drug ineffective, 1/5 cardiac event

Report ID	Low level term (LLT)	Preferred Term (PT)	System Organ class (SOC)	Source
DE-SIN-2016-08-10-119	Drug effect diminished	Drug effect decreased	General disorders and administration site conditions	Spontaneous report received from the market
US-SIN-2018-05-21-72	Lack of drug effect, Hypotensive	Drug ineffective Hypotension	General disorders and administration site conditions, Vascular disorders	Report detected from literature and recorded principally for signal detection purposes
JP-SIN-2018-10-22-139	Lack of drug effect, Maternal exposure during pregnancy	Drug ineffective Maternal exposure during pregnancy	General disorders and administration site conditions Injury, poisoning and procedural complications	Report detected from literature and recorded principally for signal detection purposes
FR-SIN-2018-10-20-140	Lack of drug effect	Drug ineffective	General disorders and administration site conditions	Report detected from literature and recorded principally for signal detection purposes
JP-SIN-2018-10-29-143	ST segment elevation, Coronary artery spasm, Pneumomediastinum	Electrocardiogram ST segment elevation, Arteriospasm coronary, Pneumomediastinum	Investigations, Cardiac disorder, Respiratory, thoracic and mediastinal disorders	Report detected from literature and recorded principally for signal detection purposes

Dr. Bazini reviewed the new information and noted that there no new safety signals.

Outstanding or Unresolved Issues

I agree with the review team that there are no safety issues identified that would preclude approval of this application.

9. Advisory Committee Meeting

An advisory committee meeting was determined to not be necessary during the review of this application as there were no issues identified that would require discussion at an advisory committee.

10. Pediatrics

The requirements for pediatric studies under the Pediatric Research Equity Act of 2003 (PREA) are not applicable, because the application did not propose a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

There were no other relevant regulatory issues.

12. Labeling

Consultations were obtained from the Division of Medication Error Prevention and Analysis, and Division of Pediatric and Maternal Health. Their recommendations were incorporated into the product's labeling.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval of the 0.1 mg/mL presentation.

Risk:Benefit Assessment

The Applicant's product has the same risk:benefit as the referenced drug, Vazculep. I concur with the review team that the 0.1 mg/mL presentation may be approved.

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Requirements

None

Recommendation for other Postmarketing Study Commitments

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RIGOBERTO A ROCA
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