

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212909Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 15, 2019

To: Alla Bazini, Clinical Reviewer
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Allison Meyer, Regulatory Project Manager, (DAAAP)

Lisa Basham, Associate Director for Labeling, (DAAAP)

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP labeling comments for Biorphen (phenylephrine hydrochloride) injection, for intravenous use

NDA/BLA: NDA 212909

In response to DAAAP's consult request dated January 24, 2019, OPDP has reviewed the proposed product labeling (PI) for the original NDA/BLA submission for Biorphen (phenylephrine hydrochloride) injection, for intravenous use

PI and PPI/Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAAP on October 15, 2019, and we do not have any comments.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 2, 2019 and September 26, 2019, and our comments are provided on the proposed carton and container labeling below.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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LATOYA S TOOMBS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 26, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 212909
Product Name and Strength:	Biorphen (phenylephrine HCl) Injection, 500 mcg/5 mL (100 mcg/mL)
Applicant/Sponsor Name:	Sintetica S. A.
OSE RCM #:	2019-2807-2
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 26, 2019 for Biorphen. Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container label and carton labeling for Biorphen (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Vee S. Label and Labeling Review for Biorphen (NDA 212909). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 04. RCM No.: 2018-2807-1.

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SARAH K VEE
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IRENE Z CHAN on behalf of OTTO L TOWNSEND
09/27/2019 01:46:46 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 4, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 212909
Product Name and Strength:	Phenylephrine HCl injection, 500 mcg/5 mL (100 mcg/mL) (b) (4)
Applicant/Sponsor Name:	Sintetica S. A.
FDA Received Date:	July 31, 2019
OSE RCM #:	2018-2807-1
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 31, 2019 for phenylephrine HCl. Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container label and carton labeling for phenylephrine HCl (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

1.1 BACKGROUND

In our previous review, to address the risk that the 100 mcg/mL product may be further diluted, we recommended that Sintetica implement the following changes to the labeling for the 100 mcg/mL product:

- Container label - add the statement, (b) (4) on the principal display panel

^a Vee S. Label and Labeling Review for phenylephrine HCl (NDA 212909). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 02. RCM No.: 2018-2807.

- Replace the statement (b) (4) with (b) (4) on the principal display panel
- Carton labeling – Add a “flag” with the statement, (b) (4)

Since that time, the Office of Prescription Drug Promotion (OPDP) has raised concerns that the phrase, (b) (4) may be misleading in the description of this product. After discussion with DAAAP and after further consideration, we agree that the 100 mcg/mL product is not (b) (4). The phrase, (b) (4) implies that

(b) (4)

(b) (4) We provide recommendations below to address this concern.

In addition, we sent an information request, dated August 13, 2019, to the Applicant to provide their rationale for including the following statement on the carton labeling, (b) (4)

(b) (4) In their response on August 16, 2019, they stated that the statement is to (b) (4)

(b) (4) We searched for examples of other product labeling that currently has the (b) (4) statement. We found examples of both NDA and ANDA product labeling that contain the same statement. Thus, we find it acceptable for Biorphen labeling to include this statement and defer to DAAAP to propose revisions to this statement if they feel it is necessary.

2 CONCLUSION

The revised container label and carton labeling is unacceptable from a medication error perspective. Revised container label and carton labeling propose use of (b) (4)

(b) (4) and they propose use of (b) (4)

3 RECOMMENDATIONS FOR SINTETICA S. A.

We recommend the following be implemented prior to approval of this NDA:

Phenylephrine 500 mcg/5 mL (100 mcg/mL)

A. General Comments (Container Label and Carton Labeling)

- The proprietary and established names, BiorPHEN and PHENYLephrine, are presented with the letters ‘PHEN’ and ‘PHENYL’ capitalized. This mixed case type of presentation is typically reserved for differentiating known look-alike and sound-alike established name pairs or in rare circumstances for proprietary names to help reduce the risk of wrong drug name errors. Since Biorphen and Phenylephrine are not names that have been involved in drug name confusion or wrong drug errors, the capitalization of the letters “PHEN” and “PHENYL” are inappropriately applied. Thus, we recommend that the proprietary name and established name are presented as Biorphen and Phenylephrine.

- b. Delete the statement (b) (4) After further consideration, we have determined that your 100 mcg/mL product is not (b) (4) (b) (4)
- (b) (4) Thus, the statement (b) (4) may be misleading.
- c. (b) (4) We recommend that the "Do Not Dilute" statement be highlighted with the color background (b) (4) to ensure that the product is not diluted prior to use. In addition, we recommend the "Do Not Dilute" statement be moved directly below the strength statement.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 2, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 212909
Product Name and Strength:	Phenylephrine HCl injection, 0.5 mg/5 mL (0.1 mg mL) (b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sintetica S.A.
FDA Received Date:	December 21, 2018
OSE RCM #:	2018-2807
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Biorphen (phenylephrine HCl) injection, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the proposed Biorphen Prescribing Information (PI), carton labeling, and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION & RECOMMENDATIONS

We performed a risk assessment of the proposed PI, container labels, and carton labeling for Biorphen for areas of vulnerability that may lead to medication errors. Our review of the proposed labeling identified several areas that can be improved to increase the prominence of important information. We provide recommendations for the Division in section 3.1 and the Applicant in section 3.2 to be implemented prior to approval of the NDA.

3.1 RECOMMENDATIONS FOR THE DIVISION

Phenylephrine 0.5 mg/5 mL (0.1 mg/mL)

A. Prescribing Information

1. Dosage and Administration Section: Highlights and 2.1 General Dosage and Administration Instructions
 - a. Revise the first and second sentence to state “Phenylephrine hydrochloride Injection USP, 0.1 mg/ml is READY TO USE. No dilution is

required before administration as an intravenous bolus.” to emphasize that the product does not require dilution. We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word “not” can be overlooked and the warning may be misinterpreted as an affirmative action.

2. How Supplied/Storage and Handling Section

- a. As currently presented, the NDC numbers for this product is undefined. Submit the NDC numbers for review and ensure that the container label of one unit and the carton labeling of 10 units have different NDC package codes (last 2 digits of the NDC).

(b) (4)

3.2 RECOMMENDATIONS FOR SINTETICA S.A.

We recommend the following be implemented prior to approval of this NDA:

Phenylephrine 0.5 mg/5 mL (0.1 mg/mL)

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.
3. As currently presented, the NDC numbers for the products are represented with 'X's. For each product, submit the NDC numbers for review and ensure that the container label of one unit and the carton labeling of 10 units have different NDC package codes (last 2 digits of the NDC).
4. Revise the statement (b) (4) to state 'Recommended dosage and Directions: see Prescribing Information'.
5. We note inconsistent use of the words, "ampule" and "(b) (4)" to describe the container closure. For consistency select either word and use it throughout labeling.

B. Container Labels

1. We recommend adding the statement (b) (4) on the principal display panel to minimize the risk of the product being diluted.
2. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to the container label as required per 21CFR 201.25(c)(2). The barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i). Additionally, the barcode should be positioned such that it does not wrap around the curvature of the ampoule.^a

C. Carton Labeling

1. Replace the statement (b) (4) with (b) (4) on the principal display panel to minimize the risk of the product being diluted. We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked and the warning may be

^a Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

misinterpreted as an affirmative action.

2. On the side panel, relocate the concentration statement (i.e., “0.1 mg/mL”) that immediately follows the product name such that the concentration statement immediately follows the strength statement.
3. For the first six months of the product’s launch, consider adding a (b) (4) to the carton labeling that informs the user of this (b) (4). For example, (b) (4)

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Biorphn received on December 21, 2018 from Sintetica S.A., and the listed drug (LD).

Table 2. Relevant Product Information for Biorphn and the Listed Drug		
Product Name	Biorphn	Vazculep^b
Initial Approval Date	N/A	June 27, 2014
Active Ingredient	phenylephrine HCl	Phenylephrine HCl
Indication	for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.	
Route of Administration	Intravenous injection	
Dosage Form	injection	
Strength	0.5 mg/5 mL (0.1 mg/mL) (b) (4)	10 mg/mL
Dose and Frequency	The recommended initial dose is 40 to 100 mcg administered by intravenous bolus. May administer additional boluses every 1-2 minutes as needed; not to exceed a total dosage of 200 mcg. (b) (4) Adjust dosage according to the blood pressure goal.	Bolus intravenous injection: 40 mcg to 100 mcg every 1-2 minutes as needed, not to exceed 200 mcg. Intravenous infusion: 10 mcg/min to 35 mcg/min, titrating to effect, not to exceed 200 mcg/min. The dose should be adjusted according to the pressor response (i.e., titrate to effect)
How Supplied	0.1 mg/mL: 5 mL ampoule (supplied in packages of 10) (b) (4)	1 mL vial; for single use (supplied in packages of 25) 5 mL vial; Pharmacy Bulk Package (supplied in packages of 10)

^b Vazculep [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 JUN 17. Available from: <https://dailymed.nlm.nih.gov/dailymed/druginfo.cfm?setid=9bb87e44-0148-11e4-9191-0800200c9a66>.

		10 mL vial; Pharmacy Bulk Package (supplied as a single unit)
Storage	20°C to 25°C (68°F to 77°F), [see USP Controlled Room Temperature]	20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] Protect from light.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Biorphn labels and labeling submitted by Sintetica S.A..

- Container label received on December 21, 2018
- Carton labeling received on December 21, 2018
- Prescribing Information (Image not shown) received on December 21, 2018

B.2 Label and Labeling Images



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Review

Date: August 29, 2019 **Date consulted:** March 21, 2019

From: Carrie Ceresa, Pharm D., MPH, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Drug: BiorPHEN (phenylephrine hydrochloride injection, 0.1 mg/ml)

NDA: 212909

Applicant: Sintetica S.A.

Subject: Pregnancy and Lactation Labeling Formatting Recommendations

Proposed
Indication: for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia

Materials
Reviewed:

- December 21, 2018, submission of NDA 212909 for phenylephrine hydrochloride injection, a 505(b)(2) New Drug Application
- March 21, 2019, DPMH consult for PLLR labeling recommendations, DARRTS Reference ID 4407197

- February 6, 2014, DPMH consult, phenylephrine hydrochloride injection, 1%, NDA 204300, Miriam Dinatale, D.O., DARRTS Reference ID 3449315¹

Consult Question: “This submission contains a PLLR label. Please review the PLLR.”

INTRODUCTION AND BACKGROUND

On December 21, 2018, Sintetica S.A., submitted a 505(b)(2) New Drug Application (NDA 212090) for phenylephrine hydrochloride injection, 0.1 mg/ml relying on the FDA-approved drug product Vazculep (NDA 214300) for approval. Vazculep was initially approved in the US on June 27, 2014. Intravenous phenylephrine had been used for decades without being approved by the FDA.

The proposed indication is for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) on March 21, 2019, to assist with the Pregnancy and Lactation subsections of labeling.

¹ The referenced phenylephrine review was part of the materials reviewed but were not sources relied upon for the labeling recommendations below. Although there is overlap in the labeling proposed for the current product and labeling that appears in approved phenylephrine product labeling, the labeling recommendations in this review are based on DPMH’s independent analysis of the underlying data.

² Applicant’s Proposed Phenylephrine Injection Product Insert

REVIEW

PREGNANCY

Hypotension during anesthesia and Pregnancy

- Hypotension is a common side effect during spinal anesthesia during cesarean delivery.³
- The use of vasopressors, such as ephedrine and phenylephrine, to prevent or treat hypotension during spinal anesthesia for cesarean delivery is standard of care.³
- According to an updated report by the American Society of Anesthesiologist Task Force on Obstetric Anesthesia and The Society for Obstetric Anesthesia and Perinatology, ephedrine or phenylephrine IV may be used for treating hypotension during neuraxial anesthesia.⁴
- According to the American College of Obstetricians and Gynecologists, approximately 10% of women will develop hypotension with low-dose neuraxial labor analgesia that can be prevented by preloading with or administering small doses of vasopressors, such as ephedrine or phenylephrine, IV.⁵

Nonclinical Experience

Animal reproduction studies have not been conducted. Published studies in normotensive pregnant rabbits report early onset labor, increased fetal lethality, and adverse placental effects with subcutaneous phenylephrine administration during gestation at doses approximately 1.9-times the total daily human dose. Published studies in normotensive pregnant sheep report decreased uterine blood flow and decreased PaO₂ in the fetus with intravenous phenylephrine administration during late gestation at doses less than and similar to the human dose. The reader is referred to the full Pharmacology/Toxicology review by Dan Mellon, Ph.D., DARRTS.

³ Kinsella SM et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anesthesia. *Anesthesia*, 2018, 72:71-92.

⁴ Practice Guidelines for Obstetric Anesthesia. An updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology, *Anesthesiology*, 2016, 124 (2):1-31.

⁵ ACOG Practice Bulletin 209 (replaces practice bulletin 177). *Obstetric Analgesia and Anesthesia*. 2019, 133(3):e208-e225.

Review of Literature

Applicant's Review of Literature

The applicant provided a summary available published literature with regard to the use of phenylephrine as a vasopressor for prevention and treatment of maternal hypotension after regional anesthesia during caesarean section. Overall, published literature implies that phenylephrine use in a hypotension setting of anesthesia is well tolerated. Reviewed data are based on studies with exposures that occurred at the time of caesarean delivery, and these studies have not identified an adverse effect on maternal outcomes or infant Apgar scores. The most commonly reported side effect during delivery in patients treated with phenylephrine exposure are bradycardia and hypertension. No difference was seen in bolus doses versus intravenous infusion and no detrimental effects were observed in the neonates.^{6,7,8,9,10,11,12} See summary Table 1 in Appendix A for specific information from each publication on maternal associated hemodynamic adverse events after phenylephrine exposure with caesarian section. Published literature also suggests a decrease in maternal cardiac outcome with phenylephrine administration perioperatively which is thought to be caused directly by the decrease in heart rate.^{7,13,14}

Additionally, nausea and vomiting are commonly reported during anesthesia and the authors conclude both are linked to hypotension. According to published literature nausea and vomiting are both correlated with control of hypotension. For example, women with the lowest phenylephrine infused dose had the highest incidence of hypotensive nausea and vomiting

⁶ Allen T et al., A Double-Blind, Placebo-Controlled Trial of Four Fixed Rate Infusion Regimens of Phenylephrine for Hemodynamic Support During Spinal Anesthesia for Cesarean Delivery. *Anesth Analg*, 2010, 111:1221-9.

⁷ Doherty A et al. Phenylephrine Infusion Versus Bolus Regimens During Cesarean Delivery Under Spinal Anesthesia: A Double-Blind Randomized Clinical Trial to Assess Hemodynamic Changes, *Anesth Analg*, 2012, 115:1343-50.

⁸ Mohta M et al. Effect of different phenylephrine bolus doses for treatment of hypotension during spinal anesthesia in patients undergoing elective caesarean section. *Anaesth Intensive Care*, 2015, 43(1):74-80.

⁹ Ngan Kee WD et al. Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anesthesia for non-elective caesarean section. *Anesthesia*, 2008, 63:1319-1326.

¹⁰ Thomas DG et al. Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anesthesia for caesarean section. *British Journal of Anaesthesia*, 1996, 76:61-65.

¹¹ Cooper D et al. Prospective evaluation of systolic arterial pressure control with a phenylephrine infusion regimen during spinal anaesthesia for caesarean section, *International Journal of Obstetric Anaesthesia*, 2012, 21:245-252.

¹² Ngan Kee WD et al. Placental Transfer and Fetal Metabolic Effects of Phenylephrine and Ephedrine during Spinal Anesthesia for Cesarean Delivery. *Anesthesiology*, 2009, 111:506-12.

¹³ Dyer R et al. Hemodynamic Effects of Ephedrine, Phenylephrine, and the Coadministration of Phenylephrine with Oxytocin during Spinal Anesthesia for Elective Cesarean Delivery. *Anesthesiology*, 2009, 111:753-65.

¹⁴ Stewart A et al. The Dose-Dependent Effects of Phenylephrine for Elective Cesarean Delivery Under Spinal Anesthesia. *Anesth Analg*, 2010, 111:1230-7.

episodes compared to those who received the highest doses.^{6,7,8,9,10,11,12,14,15,16,17,18,19,20,21,22,23,24,25} See Table 2 in Appendix A for specific information from each publication on nausea and vomiting occurring after phenylephrine exposure.

Fetal effects of phenylephrine exposure during delivery have also been documented in published literature such as Apgar scores and fetal blood acid-base levels. When comparing various regimens (bolus versus intravenous) of phenylephrine administration no differences were observed in neonatal acid-base levels. Additionally, fetal parameters, such as Apgar scores, were also not affected by increasing doses of phenylephrine.^{6,7,8,12,13,14,15,16,17,21,22,23,24,25,26,27} See Table 3 in Appendix A for more specific information on each publication.

DPMH's Review of Literature

DPMH conducted a search of published literature using PubMed and Embase regarding phenylephrine injection exposure during pregnancy using the following search terms, “phenylephrine injection and fetal malformations,” “phenylephrine injection and spontaneous abortion and miscarriage,” “phenylephrine injection and embryo-fetotoxicity.” In addition to the applicant’s review of literature, no additional relevant data were found for review. No additional data was found for review in Micromedex²⁸ or *Drugs in Pregnancy and Lactation* by Briggs and Freeman. Specifically, no data were found with regard to phenylephrine injection exposure during the first trimester.

¹⁵ Aragao F et al. Comparison of metaraminol, phenylephrine and ephedrine in prophylaxis and treatment of hypotension in cesarean section under spinal anesthesia. *Rev Bras Anesthesiol*, 2014, 64(5):299-306.

¹⁶ Das Neves J et al. Phenylephrine for Blood Pressure Control in Elective Cesarean Section: Therapeutic versus Prophylactic Doses. *Rev Bras Anesthesiol*, 2010, 60(4):391-398.

¹⁷ Das S et al. A comparative study of infusions of phenylephrine, ephedrine and phenylephrine plus ephedrine on maternal haemodynamics in elective caesarean section. *Indian Journal of Anaesthesia*, 2011, 55(6):578-583.

¹⁸ De Souza V et al. Effects of Prophylactic Continuous Infusion of Phenylephrine on Reducing the Mass of Local Anesthetic in Patients Undergoing Spinal Anesthesia for Cesarean Section. *Rev Bras Anesthesiol*, 2011, 61(4):409-424.

¹⁹ Gunda C et al. Vasopressor choice for hypotension in elective Cesarean section: ephedrine or phenylephrine? *Arch Med*, 2010, 2:256-263.

²⁰ Hall P et al. Spinal anaesthesia for Caesarean section: comparison of infusions of phenylephrine and ephedrine. *British Journal of Anaesthesia*, 1994, 73:471-474.

²¹ Ngan Kee WD et al. Comparison of phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia for Caesarean section. *British Journal of Anaesthesia*, 2004, 92(4):469-74.

²² Ngan Kee WD et al. Haemodynamic effects of glycopyrrolate pre-treatment before phenylephrine infusion during spinal anaesthesia for caesarean delivery. *International Journal of Obstetric Anesthesia*, 2013, 22:179-187.

²³ Sen I et al. Colloid cohydration and variable rate phenylephrine infusion effectively prevents postspinal hypotension in elective Cesarean deliveries. *Journal of Anesthesiology Clinical Pharmacology*, 2013, 29(3):348-355.

²⁴ Siddik-Sayyid S et al. A Randomized Controlled Trial of Variable Rate Phenylephrine Infusion with Rescue Phenylephrine Boluses Versus Rescue Boluses Alone on Physician Interventions During Spinal Anesthesia for Elective Cesarean Delivery. *Anesth Analg*, 2014, 118:611-8.

²⁵ Tanaka M et al. ED95 of phenylephrine to prevent spinal-induced hypotension and/or nausea at elective cesarean delivery. *International Journal of Obstetric Anesthesia*, 2009, 18:125-130.

²⁶ Prakash S et al. Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery: a randomised study. *International Journal of Obstetric Anesthesia*, 2010, 9:24-30.

²⁷ Saravanan S et al. Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in Caesarean section. *British Journal of Anaesthesia*, 2006, 96(1):95-9.

²⁸ Phenylephrine hydrochloride injection. Truven Health Analytics LLC. Micromedex.

According to Micromedex,²⁸ “There are no adequate and well-controlled studies of phenylephrine in pregnant women. Vasoconstriction of uterine vessels and reduced uterine blood flow associated with use of phenylephrine may result in fetal hypoxia. Animal studies have suggested this drug may have adverse effects, including early onset labor, increased fetal lethality, adverse placental effects, teratogenic effects, decreased uterine blood flow, and decreased PaO₂ in the fetus. Therefore, phenylephrine should only be administered to a pregnant woman if the potential benefit outweighs the potential risk to the fetus. In animal studies, early onset labor, increased fetal lethality, adverse placental effects, and potential teratogenic effects (1 incidence of clubbed feet, partial development of the intestine) were observed in normotensive pregnant rabbits administered subQ doses of 0.33 mg/kg 3 times daily (approximately 1.9-fold the total daily human dose) during gestation. Decreased uterine blood flow and decreased PaO₂ in the fetus were observed in normotensive pregnant sheep administered IV phenylephrine at doses of 4 mcg/kg/min for 30 minutes (1.1 to 1.2 times the human bolus dose based on body surface area) during late gestation.”

The reader is also referred to the previous DPMH reviews for phenylephrine products (2014)²⁹ and (2018).³⁰ The use of vasopressors to prevent or treat hypotension during spinal anesthesia for caesarian delivery is standard of care. Both ephedrine and phenylephrine have been commonly used and have been shown to be effective. Phenylephrine seems to be currently favored over ephedrine due to a lower incidence of fetal acidosis associated with phenylephrine. Neonatal Apgar scores, in most studies comparing the two agents, have been similar.

Review of Pharmacovigilance Database

The applicant identified one case in their pharmacovigilance database, which was also published in Toda et al (2018),³¹ of a 35-year-old pregnant female in Japan at 13 weeks’ gestation who underwent thoracic epidural anesthesia prior to a laparoscopic oophorectomy. The surgery was uneventful; however, following extubation and sugammadex administration, the patient developed anaphylactic shock. She was administered ephedrine and phenylephrine with no improvement. A tracheal intubation was performed as well as administration of dopamine and noradrenaline. She was then treated with adrenaline intramuscular (IM) and sent to the intensive care unit (ICU). No further information was provided. There is no information on the outcome of the fetus.

Reviewer comment: The applicant addressed the Pregnancy and Lactation Labeling Rule (PLLR) requirements. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH’s opinion of the data submission and recommendations.

²⁹ February 6, 2014, DPMH consult, phenylephrine hydrochloride injection, 1%, NDA 204300, Miriam Dinatale, D.O., DARRTS Reference ID 3449315

³⁰ May 14, 2018, DPMH consult for Promethazine HCl and Codeine Phosphate (PC) Oral Solution 6.25mg/10mg/5mL Promethazine HCl, Phenylephrine HCl and Codeine Phosphate (PPC) Oral Solution, 6.25 mg/5mg/10mg/5mL, NDA 8306, Jane Liedtka, M.D., DARRTS Reference ID 4261317

³¹ Toda H et al. A case of sugammadex-induced anaphylactic shock in a pregnant woman. Japanese Journal of Anesthesiology, 2018, 67(8):847-850.

LACTATION

Nonclinical Experience

Animal reproduction studies have not been conducted. According to the applicant, published nonclinical literature in cows following phenylephrine administration shows a reduction in milk ejection. The reader is referred to the full Pharmacology/Toxicology review by Dan Mellon, Ph.D., DARRTS.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature, and no data were found.

DPMH's Review of Literature

DPMH conducted a search of published literature using PubMed and Embase regarding phenylephrine injection exposure during lactation using the following search terms, "phenylephrine injection and lactation." No data were found. Also, there were no additional data found in *Medication and Mothers Milk*,³² or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.³³

According to LactMed,³⁴ "The oral bioavailability of phenylephrine is only about 40%, so the drug is unlikely to reach the infant in large amounts. However, intravenous or oral administration of phenylephrine might decrease milk production. Because no information is available on the use of oral phenylephrine during breastfeeding, an alternate drug may be preferred, especially while nursing a newborn or preterm infant."

Reviewer comment: The applicant addressed the PLLR requirements. There are no clinical data for review. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Studies to evaluate the effect of phenylephrine on fertility have not been conducted.

Review of Literature

The applicant and DPMH conducted a review of published literature on the effects of phenylephrine injection on females and males of reproductive potential, and no data were found.

Reviewer comment: The applicant addressed the PLLR requirements. There are no clinical data for review. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

³² Hale, Thomas. Medications and Mother's Milk. www.halesmeds.com. accessed 16 August 2019.

³³ Briggs, GG and Freeman, R., Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk Online version: <http://ovidsp.tx.ovid.com/sp-3.31.1b/ovidweb.cgi>.

³⁴ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

DISCUSSION AND CONCLUSIONS

Pregnancy

Available data from published literature that include randomized controlled clinical trial and meta-analyses with phenylephrine injection use during anesthesia for caesarian delivery for hypotension in pregnant women have not established a drug-associated risk of major birth defects and miscarriage. Available data are based on studies with exposures that occurred at the time of caesarean delivery, and these studies have not identified an adverse effect on maternal outcomes or infant Apgar scores. The reader is also referred to the previous DPMH reviews for phenylephrine products (2014)²⁹ and (2018)³⁰. The use of phenylephrine to prevent or treat hypotension during spinal anesthesia for caesarian delivery is standard of care. Both ephedrine and phenylephrine have been commonly used and are effective. Phenylephrine seems to be currently favored over ephedrine due to a lower incidence of fetal acidosis associated with phenylephrine. Neonatal Apgar scores, in most studies comparing the two agents, have been similar.

Animal reproduction studies were not conducted. Published studies in animals provide support for concern of premature births and decreased fetal weight due to vasoconstriction of blood vessels in the placenta. However, intravenous phenylephrine injection has a rapid onset and short duration of action when given during surgery and is commonly used during caesarian delivery for hypotension.

Lactation

There are no available clinical data for review. Published nonclinical literature in cows following phenylephrine administration shows a reduction in milk ejection. DPMH recommends using the standard risk/benefit language in subsection 8.2 that would allow women who are taking phenylephrine injection to breastfeed.

Females and Males of Reproductive Potential

There are no available clinical data for review. Therefore, subsection 8.3 *Females and Males of Reproductive Potential* will be omitted from the phenylephrine labeling.

RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

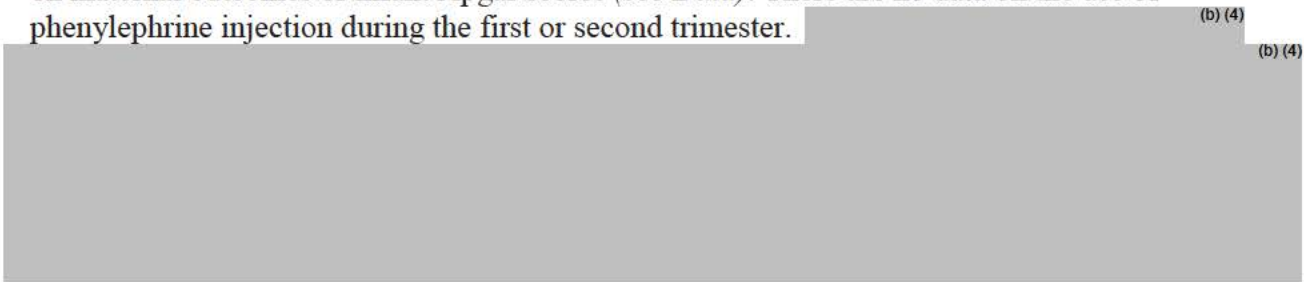
FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Data from randomized controlled trials and meta-analyses with phenylephrine hydrochloride injection use in pregnant women during caesarean section have not established a drug-associated risk of major birth defects and miscarriage. These studies have not identified an adverse effect on maternal outcomes or infant Apgar scores (*see Data*). There are no data on the use of phenylephrine injection during the first or second trimester. (b) (4)



(b) (4)

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Published randomized controlled trials over several decades, which compared the use of phenylephrine injection to other similar agents in pregnant women during cesarean section, have not identified adverse maternal or infant outcomes. In recommended doses, phenylephrine does not appear to affect fetal heart rate or fetal heart variability to a significant degree.

There are no studies on the safety of phenylephrine injection exposure during the period of organogenesis, and therefore, it is not possible to draw any conclusions on the risk of birth defects following exposure to phenylephrine injection during pregnancy. In addition, there are no data on the risk of miscarriage following fetal exposure to phenylephrine injection.

Animal Data

(b) (4)



8.2 Lactation

Risk Summary

There are no data on the presence of phenylephrine hydrochloride injection or its metabolite in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BiorPHEN and any potential adverse effects on the breastfed infant from BiorPHEN or from the underlying maternal condition

Appendix A.

Table 1. Maternal associated hemodynamics adverse events occurring after phenylephrine exposure (corresponds to Table 1, page 5-7, applicant's submission)

Author	Phenylephrine dosing (parturients number)	Hypertension	Bradycardia
Allen et al. (2010) ^a	Infusion: 25 µg/min (20) 50 µg/min (20) 75 µg/min (19) 100 µg/min (22)	25% 40% 74% 82%	15% 0% 32% 32%
Aragao et al. (2014)	Bolus plus infusion: 50 µg + 50 µg/min (30)	3%	10%
Cooper et al. (2012)	Infusion: 67 µg/min (100)	35%	2%
Das Neves et al (2010)	Infusion: 0.15 µg/kg/min (40) Prophylactic bolus: 50 µg (40) Treatment bolus: 50 µg (40)	2.5% 0% 0%	0% 2.5% 0%
Das et al. (2011)	Infusion: 66 µg/min (31)	45%	19%
De Souza et al. (2011)	Infusion: 100 µg/min (60)	26%	15%
Doherty et al. (2012) ^a	Bolus: 120 µg (30)	40% 30%	30% 36%

Author	Phenylephrine dosing (parturients number)	Hypertension	Bradycardia
Gunda et al. (2010)	<i>Bolus:</i> <i>100 µg (50)</i>	NA ^b	12%
Hall et al. (1994)	<i>Infusion:</i>	NA	20%
Mohta et al. (2015)	<i>Bolus:</i> <i>100 µg (40)</i>	15%	37.5%
Ngan Kee et al. (2004)	<i>Infusion:</i> <i>100 µg/min to maintain BP: at 80% of baseline (25)</i> <i>at 90% of baseline (25)</i>	24%	20%
		16%	32%
		21%	8%
Ngan Kee et al. (2008b)	<i>Bolus:</i> <i>100 µg</i>	NA	0%
Ngan Kee et al. (2008b)	<i>Infusion:</i> <i>100 µg/min (24)</i>	50%	13%
Ngan Kee et al. (2009)	<i>Infusion:</i> <i>100 µg/min (24)</i>	41%	12%
Ngan Kee et al. (2013)	<i>Infusion:</i> 34 µg/min (48)	16.7%	4.2%
Sen et al. (2013)	<i>Infusion:</i> 60 µg/min (45)	2.2%	4.4%
	<i>Bolus:</i> 50 µg (45)	0%	0%

Author	Phenylephrine dosing (parturients number)	Hypertension	Bradycardia
Siddik-Sayyid et al. (2014)	Infusion: 0.75 µg/kg/min	15%	18%
	Bolus (rescue): 100 µg	0%	15%
Tanaka et al., (2009)	Bolus: 40 to 120 µg (50)	28%	0%
Thomas et al. (1996)	Bolus: 100 µg (19)	NA	57%

^a Predelivery value only reported in table

^b not available or not indicated.

Table 2. Maternal nausea and vomiting occurring after phenylephrine exposure (corresponds to Table 2, page 10-12, applicant's submission)

Author	Phenylephrine dosing (parturients number)	Hypotension	Maternal nausea	Maternal vomit
Allen et al (2010) ^a	Infusion:			
	25 µg/min (20)	30%	20%	10%
	50 µg/min (20)	15%	5%	0%
	75 µg/min (19)	11%	11%	5%
	100 µg/min (22)	0%	0%	5%
Aragao et al (2013)	Bolus plus infusion: 50 µg + 50 µg/min (30)	20%	3%	3%
Cooper et al (2012)	Infusion: 67 µg/min (100)	11%	13%	0%

Author	Phenylephrine dosing (parturients number)	Hypotension	Maternal nausea	Maternal vomit
Das Neves et al (2010)	Infusion: 0.15 µg/kg/min (40)	17.5%	10%	0%
	Prophylactic bolus: 50 µg (40)	32.5%	15%	7.5%
	Treatment bolus: 50 µg (40)	85%	40%	12.5%
Das et al (2011)	Infusion: 66 µg/min (31)	NA ^b	9.7%	NA
De Souza et al (2011)	Infusion: 100 µg/min (60)	15%	1.6%	0%
Doherty et al (2012) ^a	Bolus: 120 µg (30)	23.3%	36.7% ^c	36.7% ^c
	Infusion: 120 µg/min (30)	26.7%	16.7% ^c	16.7% ^c
Gunda et al (2010)	Bolus: 100 µg (50)	NA	8%	0%
Hall et al (1994)	Infusion: 10 µg/min (10)	NA	50%	NA
Mohta et al (2015)	Bolus: 100 µg (40)	15%	2.5% ^c	2.5% ^c
	125 µg (40)	5%	5% ^c	5% ^c
	150 µg (40)	5%	5%	5% ^c

Author	Phenylephrine dosing (parturients number)	Hypotension	Maternal nausea	Maternal vomit
Ngan Kee et al (2004)	Infusion: 100 µg/min to maintain BP: at 80% of baseline (25) at 90% of baseline (25) at 100% of baseline (24)	96% 72% 29%	40% ^c 16% ^c 1% ^c	40% ^c 16% ^c 1% ^c
Ngan Kee et al (2008b)	Bolus: 100 µg	1%	3.9% ^b	3.9% ^b
Ngan Kee et al (2008b)	Infusion: 100 µg/min (24)	4%	0% ^c	0% ^c
Ngan Kee et al (2009)	Infusion: 100 µg/min (24)	4%	2% ^c	2% ^c
Ngan Kee et al (2013)	Infusion: 34 µg/min (48)	14.6%	6.3% ^c	6.3% ^c
Sen et al (2013)	Infusion: 60 µg/min (45) Bolus: 50 µg (45)	0% 75%	2.2% ^b 13.3% ^c	2.2% ^c 13.3% ^c
Siddik-Sayyid et al (2014)	Infusion: 0.75 µg/kg/min Bolus (rescue): 100 µg	20% 90%	10% ^c 44% ^c	10% ^c 44% ^c
Stewart et al (2010)	Infusion: 25 µg/min 50 µg/min 100 µg/min	36% 16% 8%	24% ^c 4% ^c 0% ^c	24% ^c 4% ^c 0% ^c
Tanaka et al (2009)	Bolus: 40 to 120 µg (50)	20%	22%	0%

Author	Phenylephrine dosing (parturients number)	Hypotension	Maternal nausea	Maternal vomit
Thomas et al (1996)	Bolus: 100 µg (19)	NA	NA	NA

^a Predelivery value only reported in table

^b not available or not indicated.

^c Nausea and vomit reported together in original publication

Table 3. Apgar scores and fetal blood umbilical artery pH after phenylephrine administration (corresponds to Table 2, page 10-12, applicant's submission)

Author	Phenylephrine dosing	Apgar score		Fetal blood umbilical artery pH ^a
Allen et al (2010)	Infusion: 25 µg/min 50 µg/min 75 µg/min 100 µg/min	1 minute 8 (8-9) 8 (8-9) 8 (8-9) 8 (8-9)	5 minutes 9 (9-9) 9 (9-9) 9 (9-9) 9 (9-9)	7.31 (7.29-7.31) 7.27 (7.25-7.30) 7.28 (7.23-7.30) 7.26 (7.24-7.29)
Aragao et al (2014)	Bolus plus infusion: 50 µg + 50 µg/min	1 minute 9 (8-9)	5 minutes 10 (9-10)	7.30 ± 0.03
Das Neves et al (2010)	Infusion: 0.15 µg/kg/min Prophylactic bolus: 50 µg Treatment bolus: 50 µg	1 minute (8-10) (8-10) (7-10)	5 minutes (9-10) (9-10) (9-10)	-
Das et al. (2011)	Infusion: 66 µg/min	1 minute (9-10)	5 minutes (9-10)	-
Doherty et al (2012)	Bolus: 120 µg Infusion: 120 µg/min	1 minute (7-10) (7-10)	5 minutes 10 10	7.28 ± 0.03 7.29 ± 0.04
Dyer et al (2009)	Bolus: 80 µg	1 minute (7-10)	5 minutes 10	7.31 ± 0.04

Author	Phenylephrine dosing	Apgar score		Fetal umbilical blood artery pH ^a
Mohta et al (2015)	Bolus: 100 µg 125 µg 150 µg	NA ^b NA		7.29 ± 0.05 7.29 ± 0.06 7.30 ± 0.06
Ngan Kee et al (2008a)	Bolus: 100 µg	NA		7.28 (7.26-7.31)
Ngan Kee et al. (2008b)	Infusion: 100 µg	1 minute ≥7	5 minutes ≥9	7.29 (7.28-7.30)
Prakash et al (2010)	Bolus: 100 µg	1 minute (8-9)	5 minutes (8-10)	7.32 ± 0.04
Saravanan et al (2005)	Infusion: 16.5 µg/min	NA		7.30 ± 0.06
Sen et al (2013)	Infusion: 60 µg/min	1 minute >7	5 minutes >7	7.27 ± 0.03
	Bolus: 50 µg	>7	>7	7.28 ± 0.03
Siddik-Sayyid et al. (2014)	Infusion: 0.75 µg/kg/min	1 minute 9 (6-10)	5 minutes 10 (9-10)	7.30 ± 0.1
	Bolus (rescue): 100 µg	9 (8-9)	10 (9-10)	7.30 ± 0.1
Stewart et al (2010)	Infusion: 25 µg/min 50 µg/min 100 µg/min	NA		7.31 ± 0.03 7.31 ± 0.04 7.30 ± 0.03
Tanaka et al (2009)	Bolus: 40 to 120 µg	NA		7.27 ± 0.05

^a Indicated as Mean value ± SD or Median value (range)

^b not available or not indicated.

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 2, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 212909
Product Name and Strength:	Phenylephrine HCl injection, 0.5 mg/5 mL (0.1 mg/mL) (b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sintetica S.A.
FDA Received Date:	December 21, 2018
OSE RCM #:	2018-2807
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Biorphen (phenylephrine HCl) injection, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the proposed Biorphen Prescribing Information (PI), carton labeling, and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION & RECOMMENDATIONS

We performed a risk assessment of the proposed PI, container labels, and carton labeling for Biorphen for areas of vulnerability that may lead to medication errors. Our review of the proposed labeling identified several areas that can be improved to increase the prominence of important information. We provide recommendations for the Division in section 3.1 and the Applicant in section 3.2 to be implemented prior to approval of the NDA.

3.1 RECOMMENDATIONS FOR THE DIVISION

Phenylephrine 0.5 mg/5 mL (0.1 mg/mL)

A. Prescribing Information

1. Dosage and Administration Section: Highlights and 2.1 General Dosage and Administration Instructions

- a. Revise the first and second sentence to state

(b) (4)

(b) (4)

(b) (4) to emphasize that the product does not require dilution. We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word “not” can be overlooked and the warning may be misinterpreted as an affirmative action.

2. How Supplied/Storage and Handling Section

- a. As currently presented, the NDC numbers for this product is undefined. Submit the NDC numbers for review and ensure that the container label of one unit and the carton labeling of 10 units have different NDC package codes (last 2 digits of the NDC).

(b) (4)

3.2 RECOMMENDATIONS FOR SINTETICA S.A.

We recommend the following be implemented prior to approval of this NDA:

Phenylephrine 0.5 mg/5 mL (0.1 mg/mL)

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.
3. As currently presented, the NDC numbers for the products are represented with 'X's. For each product, submit the NDC numbers for review and ensure that the container label of one unit and the carton labeling of 10 units have different NDC package codes (last 2 digits of the NDC).
4. Revise the statement (b) (4) to state 'Recommended dosage and Directions: see Prescribing Information'.
5. We note inconsistent use of the words, "ampule" and "(b) (4)" to describe the container closure. For consistency select either word and use it throughout labeling.

B. Container Labels

1. We recommend adding the statement (b) (4) on the principal display panel to minimize the risk of the product being diluted.
2. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to the container label as required per 21CFR 201.25(c)(2). The barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i). Additionally, the barcode should be positioned such that it does not wrap around the curvature of the ampoule.^a

C. Carton Labeling

1. Replace the statement (b) (4) with (b) (4) on the principal display panel to minimize the risk of the product being diluted. We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked and the warning may be

^a Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

misinterpreted as an affirmative action.

2. On the side panel, relocate the concentration statement (i.e., “0.1 mg/mL”) that immediately follows the product name such that the concentration statement immediately follows the strength statement.
3. For the first six months of the product’s launch, consider adding a “(b) (4)” to the carton labeling that informs the user of this (b) (4). For example, (b) (4)

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Biorphn received on December 21, 2018 from Sintetica S.A., and the listed drug (LD).

Table 2. Relevant Product Information for Biorphn and the Listed Drug		
Product Name	Biorphn	Vazculep ^b
Initial Approval Date	N/A	June 27, 2014
Active Ingredient	phenylephrine HCl	Phenylephrine HCl
Indication	for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.	
Route of Administration	Intravenous injection	
Dosage Form	injection	
Strength	0.5 mg/5 mL (0.1 mg/mL) (b) (4)	10 mg/mL
Dose and Frequency	The recommended initial dose is 40 to 100 mcg administered by intravenous bolus. May administer additional boluses every 1-2 minutes as needed; not to exceed a total dosage of 200 mcg. (b) (4) Adjust dosage according to the blood pressure goal.	Bolus intravenous injection: 40 mcg to 100 mcg every 1-2 minutes as needed, not to exceed 200 mcg. Intravenous infusion: 10 mcg/min to 35 mcg/min, titrating to effect, not to exceed 200 mcg/min. The dose should be adjusted according to the pressor response (i.e., titrate to effect)
How Supplied	0.1 mg/mL: 5 mL ampoule (supplied in packages of 10) (b) (4)	1 mL vial; for single use (supplied in packages of 25) 5 mL vial; Pharmacy Bulk Package (supplied in packages of 10)

^b Vazculep [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 JUN 17. Available from: <https://dailymed.nlm.nih.gov/dailymed/druginfo.cfm?setid=9bb87e44-0148-11e4-9191-0800200c9a66>.

		10 mL vial; Pharmacy Bulk Package (supplied as a single unit)
Storage	20°C to 25°C (68°F to 77°F), [see USP Controlled Room Temperature]	20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] Protect from light.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Biorphn labels and labeling submitted by Sintetica S.A..

- Container label received on December 21, 2018
- Carton labeling received on December 21, 2018
- Prescribing Information (Image not shown) received on December 21, 2018

B.2 Label and Labeling Images

(b) (4)



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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