CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205029Orig1s010

Trade Name:	**EPINEPHRINE**
Generic or Proper Name:	
Sponsor:	BPI LABS LLC
Approval Date:	May 12, 2023
Indication:	**EPINEPHRINE** is a non-selective alpha and beta adrenergic agonist indicated: • To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. .

CENTER FOR DRUG EVALUATION AND RESEARCH

205029Orig1s010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 205029/S-010

SUPPLEMENT APPROVAL

BPI Labs, LLC
Attention: Ravi Kumar Tirlangi
Associate Director
12393 Belcher Rd S
Suite 450
Largo, FL 33773

Dear Mr. Tirlangi:

Please refer to your supplemental new drug application (sNDA) dated and received March 19, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Epinephrine Injection, USP.

We acknowledge receipt of your amendment dated October 25, 2021, which constituted a complete response to our July 19, 2021 action letter.

This Prior Approval sNDA provides for the addition of a pre-filled syringe presentation of Epinephrine Injection, USP, 1 mg/mL, to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on April 19, 2023 and May 8, 2023, respectively, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labeling for approved NDA 205029/ S-010**." Approval of this submission by FDA is not required before the labeling is used.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[3]

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Quynh Nguyen, PharmD, RAC-US, Regulatory Project Manager at (301) 796-0510.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

[3]https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

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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/

NORMAN L STOCKBRIDGE
05/12/2023 12:56:30 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s010

OTHER ACTION LETTERS

NDA 205029/S-010

COMPLETE RESPONSE

Belcher Pharmaceuticals, LLC
Attention: Mihir Taneja
Vice President
6911 Bryan Dairy Rd
Suite 210
Largo, FL 33777

Dear Mihir Taneja:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 19, 2021, and your amendments, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Epinephrine Injection, USP 1 mg/mL.

This supplemental new drug application proposes addition of a new prefilled syringe presentation of Epinephrine Injection, USP 1 mg/mL.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Your application referenced DMF (b) (4) This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on (b) (4) These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address these deficiencies.

2. Provide the extractable/leachable study results for the proposed container closure system (i.e. glass syringe and rubber plunger). Condition of the study should represent a maximum worst case scenario. Provide toxicological risk assessment based on the extractable/leachable study results.

3. The formulation of the proposed drug product (post-change) is not qualitatively and quantitatively the same as the approved formulation (pre-change) and therefore, waiver of in vivo BA/BE study under regulation 21 CFR 320.22(b)(1) is not feasible for your proposed drug product. However, a scientific bridge between the pre-change and postchange product can be established under 21 CFR 320.24(b)(6) if adequately supported by further information and data. Submit the following information and corresponding data in support of the bridge under CFR 320.24(b)(6):

i. A side-by-side comparison of the qualitative and quantitative compositions of the proposed drug product (post-change) and the approved drug product (pre- change).
ii. Comparative physicochemical data (such as pH, osmolality, viscosity, specific gravity, color and clarity) for at least 3 production lots of the proposed drug product and 3 lots of the approved drug product. The measurements should be done in triplicate for each lot tested. For physicochemical characteristics comparison, data should be generated on both pre- and post-dilution products covering the approved diluents.
iii. Justification that any differences in the formulation and physicochemical characteristics between the proposed drug product and the approved drug product do not impact in vivo performance of your product

FACILITY INSPECTIONS

4. During a recent inspection of the BPI Labs (FEI: 3015156709) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

If you have any questions, call Elizabeth Eydelman, MPH, Regulatory Business Process Manager, at (301) 796 - 5071.

Sincerely,

{See appended electronic signature page}

Gurpreet Gill-Sangha, PhD
Branch Chief, Branch 3
Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Gurpreet
Gill Sangha

Digitally signed by Gurpreet Gill Sangha
Date: 7/19/2021 09:18:44AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s010

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPINEPHRINE INJECTION USP safely and effectively. See full prescribing information for EPINEPHRINE INJECTION USP.

EPINEPHRINE INJECTION USP, 1 mg/mL Syringe, for intravenous use
Initial U.S. Approval: 1939

----------INDICATIONS AND USAGE----------
Epinephrine is a non-selective alpha and beta adrenergic agonist indicated:
- To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. (1.1)

----------DOSAGE AND ADMINISTRATION----------
- Hypotension associated with septic shock (2.2):
  - Dilute epinephrine in dextrose solution prior to infusion.
  - Infuse epinephrine into a large vein.
  - Titrate 0.05 mcg/kg/min to 2 mcg/kg/min to achieve desired blood pressure.
  - Wean gradually.

----------DOSAGE FORMS AND STRENGTHS----------
Injection solution: 1 mg/mL Syringe. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Monitor patient for acute severe hypertension. (5.1)
- Avoid extravasation into tissues, which can cause local necrosis. (5.2)
- Potential for pulmonary edema, which may be fatal. (5.3)
- May constrict renal blood vessels and decrease urine formation. (5.4)
- May induce potentially serious cardiac arrhythmias or aggravate angina pectoris, particularly in patients with underlying heart disease. (5.5)
- Presence of sulfite in this product should not deter use. (5.7)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions to systemically administered epinephrine are headache; anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; peripheral coldness; nausea/vomiting; and/or respiratory difficulties. Arrhythmias, including fatal ventricular fibrillation, rapid rises in blood pressure producing cerebral hemorrhage, and angina have occurred. (6)

To report SUSPECTED ADVERSE REACTIONS, contact BPI Labs, LLC at (727) 471-0850 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Drugs that counter the pressor effects of epinephrine include alpha blockers, vasodilators such as nitrates, diuretics, antihypertensives, and ergot alkaloids. (7)
- Drugs that potentiate the effects of epinephrine include sympathomimetics, beta blockers, tricyclic antidepressants, MAO inhibitors, COMT inhibitors, clonidine, doxapram, oxytocin, levothyroxine sodium, and certain antihistamines. (7)
- Drugs that increase the arrhythmogenic potential of epinephrine include beta blockers, cyclopropane and halogenated hydrocarbon anesthetics, quinidine, antihistamines, exogenous thyroid hormones, diuretics, and cardiac glycosides. Observe for development of cardiac arrhythmias. (7)
- Potassium-depleting drugs, including corticosteroids, diuretics, and theophylline, potentiate the hypokalemic effects of epinephrine. (7)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm (8.1)
- Elderly patients and pregnant women may be at greater risk of developing adverse reactions when epinephrine is administered parenterally. (8.1, 8.5)

Revised: 05/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hypotension associated with Septic Shock

Epinephrine Injection USP, 1 mg/mL is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is colored or cloudy, or if it contains particulate matter. Discard any unused portion.

2.2 Hypotension associated with Septic Shock

Dilute epinephrine in 5 percent dextrose solution or 5 percent dextrose and sodium chloride solution. These dextrose containing fluids provide protection against significant loss of potency by oxidation. **Administration in saline solution alone is not recommended.** Whole blood or plasma, if indicated to increase blood volume, should be administered separately.

Add 1 mL (1 mg) of epinephrine from its Syringe to 1,000 mL of a 5 percent dextrose containing solution. Each mL of this dilution contains 1 mcg of epinephrine.

Correct blood volume depletion as fully as possible before any vasopressor is administered. When, as an emergency measure, intraaortic pressures must be maintained to prevent cerebral or coronary artery ischemia, epinephrine can be administered before and concurrently with blood volume replacement.

Whenever possible, give infusions of epinephrine into a large vein. Avoid using a catheter tie-in technique, because the obstruction to blood flow around the tubing may cause stasis and increased local concentration of the drug. Occlusive vascular diseases (for example, atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease) are more likely to occur in the lower than in the upper extremity; therefore, avoid the veins of the leg in elderly patients or in those suffering from such disorders. There is potential for gangrene in a lower extremity when infusions of catecholamine are given in an ankle vein.

To provide hemodynamic support in septic shock associated hypotension in adult patients, the suggested dosing infusion rate of intravenously administered epinephrine is 0.05 mcg/kg/min to 2 mcg/kg/min, and is titrated to achieve a desired mean arterial pressure (MAP). The dosage may be adjusted periodically, such as every 10 to 15 minutes, in increments of 0.05 mcg/kg/min to 0.2 mcg/kg/min, to achieve the desired blood pressure goal.

Continuous epinephrine infusion is generally required over several hours or days until the patient's hemodynamic status improves. The duration of perfusion or total cumulative dose cannot be predicted.

After hemodynamic stabilization, wean incrementally over time, such as by decreasing doses of epinephrine every 30 minutes over a 12- to 24-hour period.

3 DOSAGE FORMS AND STRENGTHS

Injection solution: 1 mg/mL epinephrine as a sterile solution in a 1 mL glass syringe, marked Epinephrine Injection USP, 1 mg/mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

When Epinephrine Injection is administered intravenously, titrate the infusion while monitoring vital signs. Invasive arterial blood pressure monitoring and central venous pressure monitoring are recommended. Because of varying response to epinephrine, dangerously high blood pressure may occur *[see Drug Interactions (7)]*.

5.2 Extravasation and Tissue Necrosis with Intravenous Infusion

When Epinephrine Injection is administered intravenously, the infusion site should be checked frequently for free flow. Avoid extravasation of epinephrine into the tissues, to prevent local necrosis. Blanching along the course of the infused vein, sometimes without obvious extravasation, may be attributed to vasa vasorum constriction with increased permeability of the vein wall, permitting some leakage. This also may progress on rare occasions to superficial slough. Hence, if blanching occurs, consider changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

Antidote for Extravasation Ischemia: To prevent sloughing and necrosis in areas in which extravasation has taken place, infiltrate the area with 10 mL to 15 mL of saline solution containing from 5 mg to 10 mg of phentolamine, an adrenergic blocking agent. Use a syringe with a fine hypodermic needle, with the solution being infiltrated liberally throughout the area, which is easily identified by its cold, hard, and pallid appearance. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours.

5.3 Pulmonary Edema

When Epinephrine Injection is administered intravenously, there is risk of pulmonary edema because of the peripheral constriction and cardiac stimulation produced. Treatment of pulmonary edema consists of a rapidly acting alpha-adrenergic blocking drug (such as phentolamine mesylate) and respiratory support.

5.4 Renal Impairment

Intravenously administered epinephrine initially may produce constriction of renal blood vessels and decrease urine formation.

5.5 Cardiac Arrhythmias and Ischemia

Epinephrine may induce cardiac arrhythmias and angina pectoris in patients, especially patients suffering from coronary artery disease, organic heart disease, cerebrovascular disease, hypertension, or patients who are receiving drugs that sensitize the myocardium [see *Adverse Reactions (6)* and *Drug Interactions (7)*]. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug (such as propranolol).

5.6 Other Disease Interactions

Epinephrine should be administered with caution to patients with hyperthyroidism, Parkinson's disease, diabetes mellitus, pheochromocytoma, elderly individuals, and pregnant women. Patients with Parkinson's disease may experience psychomotor agitation or notice a temporary worsening of symptoms. Diabetic patients may experience transient increases in blood sugar. Despite these concerns, the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.

5.7 Allergic Reactions Associated with Sulfite

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of sulfite(s) in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

6 ADVERSE REACTIONS

The following adverse reactions associated with the infusion of epinephrine were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Cardiovascular disorders: tachycardia, supraventricular tachycardia, ventricular arrhythmias, myocardial ischemia, myocardial infarction, limb ischemia, pulmonary edema
Gastrointestinal disorders: Nausea, vomiting
General disorders and administrative site conditions: Chest pain, extravasation,
Metabolic: hypoglycemia, hyperglycemia, insulin resistance, hypokalemia, lactic acidosis
Nervous system disorders: Headache, nervousness, paresthesia, tremor, stroke, central nervous system bleeding
Psychiatric disorders: Excitability
Renal disorders: Renal insufficiency
Respiratory: Pulmonary edema, rales
Skin and subcutaneous tissue disorders: Diaphoresis, pallor, piloerection, skin blanching, skin necrosis with extravasation

7 DRUG INTERACTIONS

Drugs antagonizing pressor effects of epinephrine

- α-blockers, such as phentolamine
- Vasodilators, such as nitrates
- Diuretics
- Antihypertensives
- Ergot alkaloids

Drugs potentiating pressor effects of epinephrine

- Sympathomimetics
- β-blockers, such as propranolol
- Tricyclic anti-depressants
- Monoamine oxidase (MAO) inhibitors
- Catechol-O-methyl transferase (COMT) inhibitors, such as entacapone
- Clonidine
- Doxapram
- Oxytocin

Drugs potentiating arrhythmogenic effects of epinephrine.

Patients who are concomitantly receiving any of the following drugs should be observed carefully for the development of cardiac arrhythmias [see *Warnings and Precautions (05.5)* and *Adverse Reactions (6)*].

- β-blockers, such as propranolol
- Cyclopropane or halogenated hydrocarbon anesthetics, such as halothane
- Antihistamines
- Thyroid hormones
- Diuretics
- Cardiac glycosides, such as digitalis glycosides
- Quinidine

Drugs potentiating hypokalemic effects of epinephrine

- Potassium depleting diuretics
- Corticosteroids
- Theophylline

Epinephrine should not be used to counteract circulatory collapse or hypotension caused by phenothiazines, as a reversal of the pressor effects of epinephrine may result in further lowering of blood pressure.

Epinephrine may antagonize the neuronal blockade produced by guanethidine resulting in decreased antihypertensive effect and requiring increased dosage of the latter.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged experience with epinephrine use in pregnant women over several decades, based on published literature, does not identify a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, there are risks to the mother and fetus associated with epinephrine use during labor or delivery (see *Clinical Considerations*). In animal reproduction studies, epinephrine administered by the subcutaneous route to pregnant rabbits, mice, and hamsters, during the period of organogenesis, resulted in adverse developmental effects (including gastroschisis, embryonic lethality, and delayed skeletal ossification) at doses approximately 2 times the maximum recommended daily intramuscular, subcutaneous, or intravenous dose (see *Data*).

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 United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypotension associated with septic shock is a medical emergency in pregnancy which can be fatal if left untreated. Delaying treatment in pregnant women with hypotension associated with septic shock may increase the risk of maternal and fetal morbidity and mortality. Life-sustaining therapy for the pregnant woman should not be withheld due to potential concerns regarding the effects of epinephrine on the fetus.

Labor or Delivery

Epinephrine usually inhibits spontaneous or oxytocin-induced contractions of the pregnant human uterus and may delay the second stage of labor. Avoid epinephrine during the second stage of labor. In dosage sufficient to reduce uterine contractions, the drug may cause a prolonged period of uterine atony with hemorrhage. Avoid epinephrine in obstetrics when maternal blood pressure exceeds 130/80 mmHg.

Although epinephrine may improve maternal hypotension associated with septic shock and anaphylaxis, it may result in uterine vasoconstriction, decreased uterine blood flow, and fetal anoxia.

Data

Animal Data

In an embryofetal development study with pregnant rabbits dosed during the period of organogenesis (on days 3 to 5, 6 to 7, or 7 to 9 of gestation), epinephrine caused teratogenic effects (including gastroschisis) at doses approximately 15 times the maximum recommended intramuscular, subcutaneous, or intravenous dose (on a mg/m^2 basis at a maternal subcutaneous

dose of 1.2 mg/kg/day for 2 to 3 days). Animals treated on days 6 to 7 had decreased number of implantations.

In an embryofetal development study, pregnant mice were administered epinephrine (0.1 to 10 mg/kg/day) on Gestation Days 6 to 15. Teratogenic effects, embryonic lethality, and delays in skeletal ossification were observed at approximately 3 times the maximum recommended intramuscular, subcutaneous, or intravenous dose (on a mg/m^2 basis at maternal subcutaneous dose of 1 mg/kg/day for 10 days). These effects were not seen in mice at approximately 2 times the maximum recommended daily intramuscular or subcutaneous dose (on a mg/m^2 basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

In an embryofetal development study with pregnant hamsters dosed during the period of organogenesis from gestation days 7 to 10, epinephrine produced reductions in litter size and delayed skeletal ossification at doses approximately 2 times the maximum recommended intramuscular, subcutaneous, or intravenous dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 mg/kg/day).

8.2 Lactation

Risk Summary

There is no information regarding the presence of epinephrine in human milk or the effects of epinephrine on the breastfed infant or on milk production. However, due to its poor oral bioavailability and short half-life, epinephrine exposure is expected to be very low in the breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of epinephrine in pediatric patients with septic shock have not been established.

8.5 Geriatric Use

Clinical studies of epinephrine for the treatment of hypotension associated with septic shock did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients. Overdosage may also result in pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Epinephrine overdosage may also cause transient bradycardia followed by tachycardia and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by

atrial tachycardia and occasionally by atrioventricular block. Myocardial ischemia and infarction, cardiomyopathy, extreme pallor and coldness of the skin, metabolic acidosis due to elevated blood lactic acid levels, and renal insufficiency and failure have also been reported.

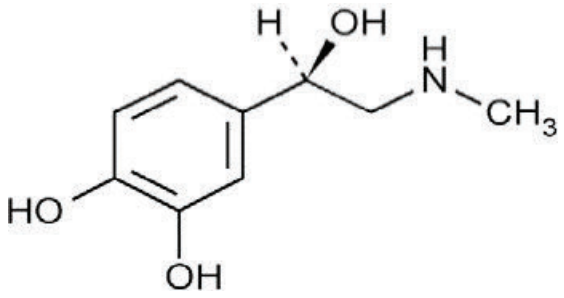
Epinephrine is rapidly inactivated in the body and treatment following overdose is primarily supportive. Treatment of pulmonary edema consists of a rapidly acting alpha-adrenergic blocking drug (such as phentolamine mesylate) and respiratory support. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug (such as propranolol). If necessary, pressor effects may be counteracted by rapidly acting vasodilators (such as nitrites) or alpha-adrenergic blocking drugs. If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug.

11 DESCRIPTION

Epinephrine Injection USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as a 1 mL solution in a 1 mL single dose syringe. Each mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 8.6 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid for pH adjustment and water for injection. The pH range is 2.2-5.0.

Solution must be diluted prior to intravenous use.

Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol. The chemical structure of epinephrine is:



The molecular weight of epinephrine is 183.2.
Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epinephrine acts on both alpha (α)- and beta (β)-adrenergic receptors. The mechanism of the rise in blood pressure is 3-fold: a direct myocardial stimulation that increases the strength of ventricular contraction (positive inotropic action), an increased heart rate (positive chronotropic action), and peripheral vasoconstriction.

12.2 Pharmacodynamics

Intravenous use for hypotension associated with septic shock

Following intravenous administration of epinephrine, increases in systolic blood pressure and heart rate are observed. Decreases in systemic vascular resistance and diastolic blood pressure are observed at low doses of epinephrine because of β_2-mediated vasodilation, but are overtaken by α_1-mediated peripheral vasoconstriction at higher doses leading to increase in diastolic blood pressure. The onset of blood pressure increase following an intravenous dose of epinephrine is < 5 minutes and the time to offset blood pressure response occurs within 20 min. Most vascular beds are constricted including renal, splanchnic, mucosal and skin.

12.3 Pharmacokinetics

When administered parenterally, epinephrine has a rapid onset and short duration of action.

Following intravenous injection, epinephrine is rapidly cleared from the plasma with an effective half-life of < 5 min. A pharmacokinetic steady state following continuous intravenous infusion is achieved within 10-15 min. In patients with septic shock, epinephrine displays dose-proportional pharmacokinetics in the infusion dose range of 0.03 to 1.7 mcg/kg/min.

Epinephrine is extensively metabolized with only a small amount excreted unchanged.

Epinephrine is rapidly degraded to vanillylmandelic acid, an inactive metabolite, by monoamine oxidase and catechol-O-methyltransferase that are abundantly expressed in the liver, kidneys and other extraneuronal tissues. The tissues with the highest contribution to removal of circulating exogenous epinephrine are the liver (32%), kidneys (25%), skeletal muscle (20%), and mesenteric organs (12%).

Special Populations

Elderly

In a pharmacokinetic study of 45-minute epinephrine infusions given to healthy men aged 20 to 25 years and healthy men aged 60 to 65 years, the mean plasma metabolic clearance rate of epinephrine at steady state was greater among the older men (144.8 versus 78 mL/kg/min for a 14.3 ng/kg/min infusion).

Body Weight

Body weight has been found to influence epinephrine pharmacokinetics. Higher body weight was associated with a higher plasma epinephrine clearance and a lower concentration plateau.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of epinephrine have not been conducted.

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro*. Epinephrine was positive in the *Salmonella* bacterial reverse mutation assay, positive in the mouse lymphoma assay, and negative in the *in vivo* micronucleus assay. Epinephrine is an oxidative mutagen based on the *E. coli* WP2 Mutoxitest bacterial reverse mutation assay. This

should not prevent the use of epinephrine under the conditions noted under the Indications and Usage.

The potential for epinephrine to impair reproductive performance has not been evaluated, but epinephrine has been shown to decrease implantation in female rabbits dosed subcutaneously with 1.2 mg/kg/day (15-fold the highest human intramuscular or subcutaneous daily dose) during gestation days 3 to 9.

13.2 Animal Toxicology and/or Pharmacology

Epinephrine was associated with metabolic effects, decreased mesentery, coronary and renal conductance in a sheep model of septic shock. Data from hemolysis study have shown that epinephrine at 1:1000 dilution is non-hemolytic. Epinephrine infusion significantly increased the MAP (69 vs. 86 mmHg) and cardiac output (6.4 vs. 7.1 L/min) and decreased renal blood flow (330 vs. 247 mL/min).

14 CLINICAL STUDIES

14.1 Hypotension associated with Septic Shock

Fourteen clinical studies from the literature documented that epinephrine increases the mean arterial pressure (MAP) in patients with hypotension associated with septic shock.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each carton contains 10 single-dose prefilled syringes containing 1 mL of a 1 mg/mL epinephrine injection, USP solution in a clear glass syringe.

NDC 54288-117-10 10 Single-Dose Prefilled Syringes Containing 1 mL

Epinephrine is light sensitive. Protect from light until ready to use.

Do not refrigerate. Protect from freezing.

Store at room temperature, between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.) Protect from alkalis and oxidizing agents.

Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.

Revised: May 2023

Manufactured by:
BPI Labs LLC
12393 Belcher Rd S, Suite 450,
Largo, FL 33773

L11I
D-2304

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s010

DIVISION DIRECTOR MEMO

DIVISION OF CARDIOLOGY AND NEPHROLOGY

Divisional Memorandum

NDA: 214439 (epinephrine injection)

Sponsor: BPI Labs, LLC

Reviewer: N. Stockbridge, M.D., Ph.D.

The product is epinephrine 1 mg/mL in a prefilled syringe. The application received a Complete Response on 19 July 2021 for issues relating to product quality and facilities. The supplement was resubmitted 25 October 2021, addressing manufacturing issues satisfactorily, and revised labeling was submitted 20 January 2023. Labeling was reviewed by DPACC, DMEPA, and OPQ (see RPM overview for details).

The review team and I concur on approval.

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/s/

NORMAN L STOCKBRIDGE
05/11/2023 08:50:10 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s010

CLINICAL REVIEW(S)

RPM Overview – *AP Action*
NDA 205029/S-010
Epinephrine Injection, USP
1 mg/10 mL (0.1 mg/mL)

Applicant:	BPI Labs, LLC
Classification:	Standard
Letter Date:	March 19, 2021
User Fee Receipt Date:	March 19, 2021
Complete Response Date:	July 19, 2021
Resubmission Date:	October 25, 2021
User Fee Goal Date:	February 25, 2022

Background
NDA 205029 for Epinephrine Injection USP, 1 mg/mL, in a 2 mL single-use ampule was approved on July 29, 2014 to increase mean arterial blood pressure in hypotension associated with septic shock. Additional indications that were subsequently approved in efficacy supplements included for the induction and maintenance of mydriasis during intraocular surgery (approved in S-001 on October 23, 2015) and for the emergency treatment of allergic reactions (Type I), including anaphylaxis (approved in S-002 on February 11, 2016).

On February 4, 2022, a chemistry, manufacturing and controls (CMC) supplement (S-009) was approved for the multi-dose vial (MDV) presentation of Epinephrine Injection USP, 10 mg/10 mL (1 mg/mL). Because the multi-dose vial presentation (b) (4) (b) (4) (b) (4)

On March 19, 2021, the Applicant (then Belcher Pharmaceuticals, LLC; now BPI Labs, LLC) submitted a prior approval CMC supplement for the addition of a new pre-filled syringe (PFS) presentation of Epinephrine Injection USP, 1 mg/mL (S-010). The PFS presentation included labeling (b) (4) he intravenous (IV) injection for the indication to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock (b) (4)

The Office of Pharmaceutical Quality (OPQ) initially agreed to manage the supplement (S-010) and issued a Complete Response (CR) letter on July 19, 2021. Deficiencies identified by the biopharmaceutics and microbiology reviewers as well as related to the facility were communicated in the CR Letter as follows:

PRODUCT QUALITY

1. Your application referenced DMF (b) (4) This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on (b) (4) These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address these deficiencies.

2. Provide the extractable/leachable study results for the proposed container closure system (i.e., glass syringe and rubber plunger). Condition of the study should represent a maximum worst case scenario. Provide toxicological risk assessment based on the extractable/leachable study results.

3. The formulation of the proposed drug product (post-change) is not qualitatively and quantitatively the same as the approved formulation (pre-change) and therefore, waiver of in vivo BA/BE study under regulation 21 CFR 320.22(b)(1) is not feasible for your proposed drug product. However, a scientific bridge between the pre-change and postchange product can be established under

21 CFR 320.24(b)(6) if adequately supported by further information and data. Submit the following information and corresponding data in support of the bridge under CFR 320.24(b)(6):

i. A side-by-side comparison of the qualitative and quantitative compositions of the proposed drug product (post-change) and the approved drug product (pre-change).

ii. Comparative physicochemical data (such as pH, osmolality, viscosity, specific gravity, color and clarity) for at least 3 production lots of the proposed drug product and 3 lots of the approved drug product. The measurements should be done in triplicate for each lot tested. For physicochemical characteristics comparison, data should be generated on both pre- and post-dilution products covering the approved diluents.

iii. Justification that any differences in the formulation and physicochemical characteristics between the proposed drug product and the approved drug product do not impact in vivo performance of your product

FACILITY INSPECTIONS

4. During a recent inspection of the BPI Labs (FEI: 3015156709) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Please refer to the CR letter and the OPQ reviews in Platform for this first review cycle.

The Applicant resubmitted the supplement on October 25, 2021.

On February 23, 2022, OPQ asked the Division of Pulmonology, Allergy, and Critical Care Products (DPACC) to review the proposed labeling change to (b) (4) As requested by DPACC, OPQ sent multiple information requests (IRs) to the Applicant requesting justification for their proposal to (b) (4) Responses to the IRs were submitted by the Applicant on March 1, 2022 and March 15, 2022. The following is excerpted from the DPACC Medical Officer Review by Dr. Jennifer Lan dated April 27, 2022 (see DARRTS for the full review):

> In summary, the Sponsor acknowledged that the (b) (4) (b) (4)
>
> DPACC reviewed the above justification and agrees with proposed (b) (4) (b) (4) if the CMC data is sufficient, but requests that a Sponsor comment be sent to (b) (4) (b) (4) This was relayed to [OPQ] who relayed they will send the following comment below in a General Advice Letter:
>
> 1. We acknowledge your Information Request responses sent on March 1 and 15, 2022 regarding your plan to (b) (4) (b) (4)

On May 26, 2022, OPQ contacted the Division of Cardiology and Nephrology (DCN) and suggested that DCN manage the supplement going forward as the OPQ review is almost complete, except for the labeling aspects involving the (b) (4) DCN took over management of the supplement from that

point forward. Regarding the labeling, the Applicant had submitted on February 15, 2022 draft labeling for the prescribing information (PI), carton and container, which had been amended to include the labeling changes approved in CMC supplement S-009 on February 4, 2022. On June 1, 2022 in response to a DCN inquiry, OPQ confirmed that there were no labeling reviews of the February 15, 2022 labeling submission, other than DPACC's clinical review dated April 27, 2022.

Upon reviewing the proposed labeling changes, DCN requested clarification from the Applicant on June 23, 2022 regarding the revised PI, carton and container submitted on February 15, 2022 that had been amended to include the labeling changes approved in CMC supplement S-009. Specifically, the Applicant was asked to clarify whether the only change from the last submitted version was the text under (b) (4) in the tracked Word version that was submitted. Additionally, the Applicant was asked to submit an annotated version of the draft carton and container labeling showing the differences between the February 15, 2022 version and the version that was previously submitted to that in supplement S-010. The Applicant responded on July 5, 2022 that the changes that they had made were only to match those changes which were approved in CMC supplement S-009 on February 25, 2022. However, one (b) (4) section (b) (4) (b) (4) had been removed from the proposed PFS labeling because the (b) (4) (b) (4) therefore, this (b) (4) section was not applicable for the (b) (4)

On January 13, 2023, DCN requested that the Applicant submit revised labeling for the PI to incorporate the addition of the (b) (4) (b) (4) On January 20, 2023, the Applicant submitted a revised PI that provided for a (b) (4) (b) (4)

In addition, in response to a clarification question by DCN on January 18, 2023 to confirm whether there were any changes being proposed to the draft carton and container labeling since the last submitted annotated versions that were submitted on June 30, 2022, the Applicant included updated carton and container labeling in the January 20, 2023 submission, with an annotated document showing their revisions to the versions previously submitted on June 30, 2022. **Note:** The updated syringe label had included (b) (4) in response to OPQ's previous communication from DPACC to the Applicant.

During the first review cycle for this supplement, DMEPA had previously reviewed the draft labeling on June 24, 2021 and July 16, 2021; refer to DARRTS for DMEPA's completed reviews by Dr. Maximilian Straka. On January 23, 2023, DCN contacted DMEPA to review the updated PI, carton and container labeling that was submitted on January 20, 2023 for the resubmission. On January 26, 2023, an internal meeting was scheduled by DCN at DMEPA's request to discuss DMEPA's questions and concerns with what was added as part of the supplement for the PFS presentation. On February 3, 2023, DMEPA requested another meeting to further discuss their concerns, specifically with labeling the PFS for an (b) (4) (b) (4) The internal meeting was subsequently scheduled by DCN and held with DCN, DMEPA and DPACC on February 28, 2023. The following is excerpted from DMEPA's review by Dr. Jody Kundreskas dated April 14, 2023 (see DARRTS for the full review):

> We noted that since our last review (see Appendix B) (b) (4) (b) (4)

(b) (4)

We met with the Division of Cardiology and Nephrology and the Division of Pulmonary, Allergy and Critical Care (DPACC) to discuss (b) (4) (b) (4)

Following this internal meeting, in her DPACC memo dated March 20, 2023, Dr. Lan wrote the following (see DARRTS for the full review):

Recommendation
DPACC reviewed the above labeling (b) (4) identified by DMEPA. DPACC is particularly (b) (4) which would be difficult to (b) (4) with the proposed (b) (4) DPACC agrees with DCN and DMEPA to (b) (4)

Thus, DCN requested that the Applicant submit revised labeling for the PFS presentation to include (b) (4) the intravenous injection for the indication to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. DCN conveyed that their current thinking was based upon further discussions with DMEPA and DPACC and stemmed (b) (4) (b) (4) (b) (4) Therefore, DCN requested that the Applicant (b) (4) (b) (4) for the labeling that was submitted on January 20, 2023. For the PI submitted on June 30, 2022 (b) (4) minor editorial corrections were also requested.

On April 3, 2023, the Applicant submitted revised labeling for the PI, carton and container, which was forwarded to the DPACC, DMEPA and OPQ reviewers for review. In an email dated April 10, 2023, Dr. Miya Paterniti, DPACC Team Lead, stated that they had no edits or comments to the revised labeling since (b) (4) (b) (4) In an email dated April 18, 2023, Dr. Sibaprasad Bhattacharyya, CMC reviewer in OPQ, stated that they had no changes to the revised labeling. In a review dated April 14, 2023, DMEPA provided additional comments on the revised PI, carton and container. DMEPA's labeling comments were conveyed to the Applicant on April 18, 2023. The Applicant submitted revised labeling on April 19, 2023. DMEPA reviewed this revised container label and carton labeling on April 22, 2023 and had no additional recommendations (refer to DARRTS for the full reviews by Dr. Jody Kundreskas). In an email reply dated May 2, 2023, Dr. Kundreskas confirmed that DMEPA had no further recommendations on the PI, either. Minor editorial corrections were made to the DRAFT PI submitted on April 19, 2023, which the Applicant agreed to in an email dated May 11, 2023.

Division Director Memorandum
In his Divisional memorandum dated May 11, 2023, Dr. Stockbridge stated that "…The review team and I concur on approval." (Refer to DARRTS for the memo.)

CMC Review
The CMC review by Dr. Sibaprasad Bhattacharyya (Primary Reviewer) and Dr. Ramesh Raghavachari (Secondary Reviewer) dated June 1, 2022 stated the following (refer to Platform for the full review):

> **12. Executive Summary and CMC assessment**:
> This prior approval labeling supplement was originally submitted for the addition of a new prefilled syringe (PFS) presentation of Epinephrine Injection drug product. A CRL was issued based on the deficiencies identified by biopharm and microbiology reviewers. In this resubmission, applicant has adequately addressed the issues. The responses have been evaluated by both microbiology and biopharm reviewers and found to be adequate. Facility is recommended for approval by OPMA on 02/03/2022.
>
> Clinical reviewer (OND/DPACC, Jennifer Lan) has identified that (b) (4) (b) (4) labeling of the DP and recommended for approval with comments.
>
> **13. Conclusions & Recommendations**:
> This supplement is recommended for approval with comments. Please issue an approval letter with following comments as recommended by clinical reviewer.
>
> **14. Comments/Deficiencies to be Conveyed to Applicant**:
> 1) We acknowledge your Information Request responses sent on March 1 and 15, 2022 regarding your plan (b) (4) (b) (4)

[Note: As described in the **Background** section, the above comment from DPACC was conveyed by OPQ to the Applicant. Ultimately, however, it was agreed that the PFS presentation (b) (4) intravenous injection for the indication to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock (b) (4)

Product Quality Microbiology Review
The Product Quality Microbiology review by Dr. Yan Zheng (Primary Reviewer) and Dr. Jesse Wells (Secondary Reviewer) dated December 29, 2021 stated the following conclusion: "Recommended for Approval." Refer to Platform for the full review.

Biopharmaceutics Review
The Biopharmaceutics review by Dr. Parnali Chatterjee (Primary Reviewer) and Dr. Haritha Mandula (Secondary Reviewer) dated January 31, 2022 stated the following (refer to Platform for the full review):

EXECUTIVE SUMMARY

> The original NDA 205029-ORIG-1 (dated 12/04/2012) for Epinephrine Injection, USP, 1 mg/1 mL in an ampoule container-closure was approved on 07/29/2014 under the 505 (b)(2) regulatory pathway. On 03/19/2021, the Applicant submitted a PAS/S-010 for NDA 205029-ORIG-1 to seek approval for a new container-closure (pre-filled syringe) of Epinephrine Injection, USP, 1 mg/1 mL *via* the 505 (b)(2) regulatory pathway. The submission is relying upon FDA's findings of safety and efficacy for the approved ampule product to support approval of the proposed pre-filled syringe product. However, deficiencies were noted, and a ***Complete Response Letter (CRL)*** was issued on 07/19/2021. The current resubmission addresses the deficiencies noted in the ***CRL*** dated 07/19/2021.

Recommendation:
Based on the overall data provided for compositional similarity, physico-chemical characteristics, together with the rationale for inclusion of 0.5% sodium metabisulfite (i.e., the addition of sodium metabisulfite will not have any impact on the pharmacokinetics, safety, and efficacy of epinephrine in the proposed pre-filled syringe (PFS) product for patients who are insensitive to sulfites), a scientific bridge is established between the approved ampule product and the proposed PFS product per 21CFR320.24(b)(6).

From Biopharmaceutics perspective, the NDA 205029-S010-RESUB 83 for pre-filled syringe of Epinephrine Injection, USP, 1 mg/1 mL is recommended for **APPROVAL**.

Facilities
The Office of Pharmaceutical Manufacturing Assessment (OPMA) previously evaluated the facility for this supplement and recommended approval on February 3, 2022 (refer to Dr. Bhattacharyya's CMC review dated June 1, 2022 in Platform). In an email dated April 18, 2023, Djelila Mezaache, ME, Senior Consumer Safety Officer, in OPMA confirmed that the facility (BPI LABS LLC | FEI: 3015156709) is still acceptable.

DPACC Review
Refer to the **Background** section above. For the first review cycle, DPACC had completed a review on April 27, 2022. For the resubmission, DPACC completed a follow-up memo on March 20, 2023 which stated that "DPACC reviewed the above labeling and agrees with the human factor concerns identified by DMEPA…. DPACC agrees with DCN and DMEPA to (b) (4) for the prefilled syringe presentation." (Refer to DARRTS for the full recommendation and reviews by Dr. Jennifer Lan).

DMEPA Review
Refer to the **Background** section above. For the first review cycle, DMEPA had previously reviewed the draft labeling on June 24, 2021 and July 16, 2021 (refer to DARRTS for the reviews by Dr. Maximilian Straka). For the resubmission, DMEPA identified several (b) (4) (b) (4) These concerns were discussed with DCN and (b) (4) DPACC in internal meetings, and subsequently, (b) (4) for the PFS presentation. DMEPA completed reviews on April 14, 2023 and April 22, 2023. For the revised container label and carton labeling revised labeling submitted on April 22, 2023, DMEPA had no additional recommendations (refer to DARRTS for the reviews by Dr. Jody Kundreskas). In an email reply dated May 2, 2023, DMEPA confirmed that they had no further recommendations on the PI.

RPM Summary
An Approval (AP) Letter will be drafted for Dr. Stockbridge's signature.

Quynh Nguyen, PharmD, RAC-US
Regulatory Project Manager
5-2-23; 5-8-23; 5-12-23

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/s/

QUYNH M NGUYEN
05/12/2023 12:13:43 PM

DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE MEMO

Sponsor	BPI Labs, LLC
Name of product	Epinephrine injection USP
Consulting Center	Division of Cardiology and Nephrology
DPACC Medical Officer	Jennifer Lan, MD, Division of Pulmonology, Allergy, and Critical Care (DPACC)
DPACC Team Lead	Miya Paterniti, MD, Division of Pulmonology, Allergy, and Critical Care (DPACC)
Review Due Date	March 14, 2023
Submission Type	NDA 205029, S10

Introduction

This is a follow-up DPACC clinical review to a previous DPACC clinical review (April 27, 2022) for an sNDA for injectable epinephrine CMC supplement, submitted by BPI Labs (previously Belcher pharmaceuticals), which proposes to add a 1 mg/mL prefilled syringe presentation for treatment of septic shock.

Background

The Applicant's injectable epinephrine 1 mg/mL ampule presentation currently is indicated for the treatment of septic shock, anaphylaxis, and induction and maintenance of mydriasis during intraocular surgery. A 10 mg/10 mL multi-dose vial is also available under this NDA. The multi-dose vial [redacted] (see previous review). The current supplement proposes adding a 1 mg/mL prefilled syringe presentation.

DPACC initially reviewed this sNDA upon CMC/DCN request in 2022 as the Applicant proposed the 1 mg/mL prefilled syringe for treatment of septic shock [redacted] This was because the proposed [redacted] DPACC agreed with the proposal to [redacted] but recommended the Applicant [redacted] (see previous review for details).

Current Review

(b) (4) on March 15, 2022 and (b) (4) for the current supplement (Figure 1). The labeling was reviewed by DCN and DMEPA

(b) (4)

DMEPA relayed concerns that there are (b) (4) (b) (4) Furthermore, DMEPA is concerned with (b) (4) (b) (4) (b) (4)

Recommendation

DPACC reviewed the above labeling and agrees with (b) (4) identified by DMEPA. DPACC is (b) (4) (b) (4) (b) (4) DPACC agrees with DCN and DMEPA to (b) (4)

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/s/

JENNIFER P LAN
03/20/2023 08:17:33 PM

MIYA O PATERNITI
03/20/2023 08:45:14 PM

MEDICAL OFFICER REVIEW
Division of Pulmonology, Allergy, and Critical Care Products

Application:	205029	**Application Type:**	NDA
Sponsor:	Belcher	**Name:**	epinephrine
Category:	Emergency treatment	**Route of Administration:**	(b) (4)
Medical Officer:	Jennifer Lan, M.D.	**Indication:**	(b) (4)
Team Leader:	Miya Paterniti, M.D.		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
October 25, 2021	October 25, 2021	Resubmission/After Action-Complete	S-10; SD: 83, eCTD 0082

Review Summary: This is a DPACC clinical review for an injectable epinephrine CMC supplement, submitted by Belcher, which proposes to (b) (4) The Belcher injectable epinephrine product is currently indicated:

1. To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock
2. For emergency treatment of allergic reactions (Type 1), including anaphylaxis

The mydriasis indication was removed with the approval of CMC supplement 9 (February 4, 2022) due (b) (4) (b) (4) (b) (4) Belcher submitted CMC supplement (S-010) to the Division of Cardiology and Nephrology (DCN) to modify the presentation from a vial to a pre-filled syringe and to (b) (4) on March 19, 2021 and was given a Complete Response on July 19, 2021 due to deficiencies in CMC data. A resubmission for this supplement was submitted in October 25, 2021. DCN notified DPACC on February 23, 2022, regarding the (b) (4) and DPACC was asked to weigh in (b) (4) The goal date for the resubmission was February 25, 2022, however, DCN relayed they will miss the goal date to allow time for DPACC to review the proposed labeling change.

DPACC sent multiple information requests for Belcher's to provide justification for their proposal to (b) (4) (b) (4) Responses dated 3/1/2022 and 3/15/2022). In summary, the Sponsor acknowledged that (b) (4) (b) (4)

DPACC reviewed the above justification and agrees with proposed (b) (4) if the CMC data is sufficient, but requests that a Sponsor comment be sent to (b) (4) (b) (4) This was relayed to DNC who relayed they will send the following comment below in a General Advice Letter:

1. We acknowledge your Information Request responses sent on March 1 and 15, 2022 regarding your plan to (b) (4)

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION: n/a

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/s/

JENNIFER P LAN
04/27/2022 12:35:02 PM

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s010

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	April 21, 2023
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 205029/S-010
Product Name, Dosage Form, and Strength:	Epinephrine Injection, 1 mg/mL
Applicant/Sponsor Name:	BPI Labs, LLC
TTT ID #:	2023-3434-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 19, 2023 for Epinephrine Injection. We reviewed the revised container label and carton labeling for Epinephrine Injection (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] Kundreskas, Jody. Label and Labeling Review for Epinephrine Injection (NDA 205029/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 APR 14. TTT ID No.: 2023-3434.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 19, 2023

Container labels

Carton labeling

APPEARS THIS WAY ON ORIGINAL


bpi Labs
Rx Only
NDC 54288-117-10
Epinephrine Injection, USP
1 mg/mL
For Intravenous Infusion Only
NOT for Ophthalmic Use
Dilute before Intravenous use.
Recommended Dosage: See prescribing information
Each mL contains:
1 mg epinephrine, 8.6 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid for pH adjustment and water for injection.
Note: Do not use solution if it is colored or cloudy, or if it contains particulate matter.
Prior to intravenous infusion, dilute 1 mL (1 mg) of epinephrine in 1,000 mL of a 5% Dextrose Solution or 5% Dextrose and Sodium Chloride Solution to produce a resulting concentration of 1 mcg/mL.
Store between 20°C to 25°C (68°F to 77°F).
Protect from light. Do Not Freeze.
10 Single-Dose Prefilled Syringes x 1 mL
Manufactured by:
BPI Labs, LLC
12393 Belcher Rd S, Suite 450
Largo FL 33773
USA
GTIN: 00000000000000
BATCH: LLLLL
EXP: YYYY-MM-DD
S/N: 0000000000000000
LBTC-10 D-2304

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/s/

JODY K KUNDRESKAS
04/21/2023 06:37:06 AM

HINA S MEHTA
04/22/2023 10:01:22 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	April 14, 2023
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 205029/S-010
Product Name, Dosage Form, and Strength:	Epinephrine Injection, 1 mg/mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	BPI Labs, LLC
FDA Received Date:	October 25, 2021, April 14, 2022, January 20, 2023, and April 3, 2023.
TTT ID #:	2023-3434
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

REASON FOR REVIEW

BPI Labs, LLC submitted a prior approval supplement for Epinephrine Injection to add a prefilled syringe (1 mg/mL) presentation to NDA 205029, indicated for the treatment of hypotension associated with septic shock [redacted] We reviewed the proposed Epinephrine Injection Prescribing Information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 205029 was approved on July 29, 2014, in a 1 mg/mL ampule presentation indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. On October 23, 2015, Supplement 1 was approved which authorized a new indication to induce and maintain mydriasis during intraocular surgery. Supplement 3 was approved on February 11, 2016, which authorized an additional indication for the treatment of anaphylaxis in adults and children. Supplement 9 added a 10 mg/10 mL (1 mg/mL) multiple dose vial utilizing separate Prescribing Information (PI) from the ampule presentation. The multiple-dose presentation [redacted] for the hypotension associated with septic shock and anaphylaxis indications [redacted] Supplement 10, proposing to add the 1 mg/mL prefilled syringe presentation, was initially received by the Agency on March 19, 2021. This Supplement received a Complete Response on July 19, 2021. We completed a review of the proposed labeling during that review cycle (see Appendix B). A response to the Complete Response for Supplement 10 was submitted on October 25, 2021. At that time the Division of Cardiology and Nephrology consulted the Division of Pulmonology, Allergy, and Critical Care Products (DPACC) to review the Supplement as the Applicant [redacted] On April 27, 2022, FDA asked the Applicant to consider [redacted] The Applicant submitted updated carton and container labels in line with this recommendation on January 20, 2023.

Additionally, we note that on July 28, 2022, the ownership of NDA 205029 was transferred from Belcher Pharmaceuticals, LLC (Belcher) to BPI Labs, LLC (BPI).

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 Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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

OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), carton and container labels for Epinephrine Injection to identify deficiencies that may lead to medication errors and areas of improvement.

We noted that since our last review (see Appendix B) the (b) (4) for the prefilled syringe presentation have been updated to (b) (4) (b) (4) DMEPA identified several (b) (4) (b) (4)

We met with the Division of Cardiology and Nephrology and the Division of Pulmonary, Allergy and Critical Care (DPACC) to discuss the (b) (4) (b) (4) septic shock indication via the intravenous route will be considered for this supplement. This decision was communicated to BPI Labs, LLC and on April

3, 2023 the Applicant submitted updated labeling and carton and container labels aligned with this decision.

We identified areas of the proposed PI and carton and container labels that could be revised to improve clarity, readability, and availability of important information. For the Division, we recommend removing (b) (4) throughout the PI, ensuring each dose has the (b) (4) (b) (4) referenced, clarifying the (b) (4) of the prefilled syringe and removal of the (b) (4) For the Applicant, we recommend updating the labels to clarify the (b) (4) of the prefilled syringe.

CONCLUSION & RECOMMENDATIONS

We conclude that the proposed PI, carton, and container labels for Epinephrine Injection may be improved to promote the safe use of the product. We provide specific recommendations for the Division in Section 4.1 and the Applicant in Section 4.2, below.

1.2 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. We note that the (b) (4) in the dosage prescribed for hypotension associated with septic shock and that the range contains (b) (4) (b) (4). We recommend revising the dosage information to include the unit of measure and to remove (b) (4) Change (b) (4) (b) (4) to "Titrate 0.05 mcg/kg/min to 2 mcg/kg/min…"

B. Prescribing Information

1. Dosage and Administration Section

a. In Section 2.2 we recommend removing (b) (4) and replacing it with its intended meaning to prevent confusion. Revise (b) (4) (b) (4) to "…every 10 to 15 minutes".

2. How Supplied/Storage and Handling

a. We recommend adding the net quantity of the prefilled syringes for clarity.

i. Revise (b) (4) (b) (4) to "Each carton contains 10 single-dose prefilled syringes containing 1 mL of a 1 mg/mL epinephrine injection…".

ii. Revise (b) (4) to "10 Single-Dose Prefilled Syringes Containing 1 mL"

3. (b) (4)

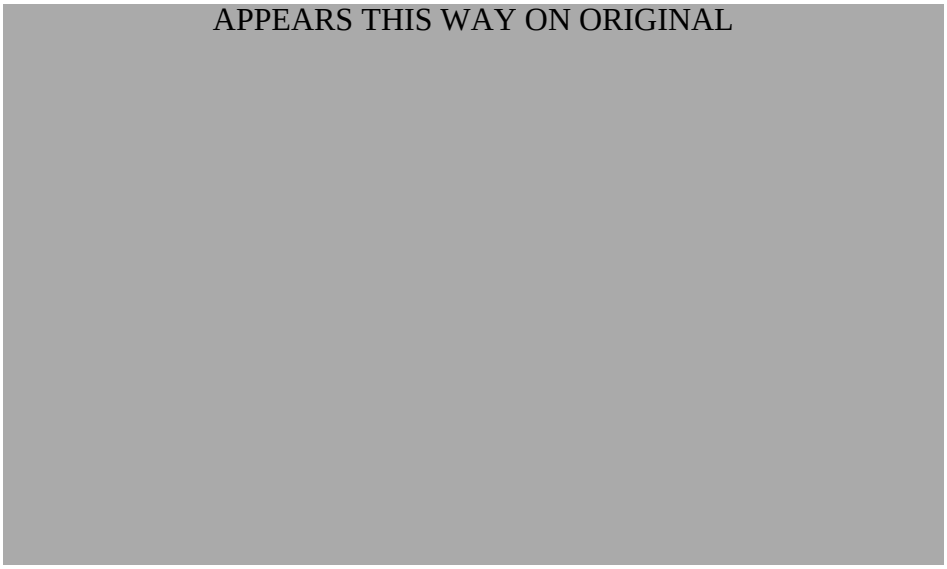
a. We recommend removal of this section to harmonize with other epinephrine products approved (b) (4) for hypotensive shock.

1.3 RECOMMENDATIONS FOR BPI LABS, LLC

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

A. General Comments
   1. The route of administration "ophthalmic" is misspelled. Revise the statement [redacted] to "NOT for Ophthalmic Use".

B. Container Labels
   1. The [redacted] does not appear on the principal display panel of the container labels. Failure to include the [redacted] on the principal display panel may result in confusion regarding the contents of the container. We recommend including a net quantity statement and ensure it is located away from and less prominent than the product strength. For example, [redacted] could be changed to "1 mL Single-Dose Prefilled Syringe" to meet this requirement.



APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Epinephrine Injection received on April 3, 2023, from BPI Labs, LLC.

Table 2. Relevant Product Information for Epinephrine Injection	
Initial Approval Date	07/29/2014
Active Ingredient	Epinephrine
Indication	**Hypotension associated with Septic Shock** Epinephrine Injection USP, 1 mg/mL is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	1 mg/mL
Dose and Frequency	**General Considerations** Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is colored or cloudy, or if it contains particulate matter. Discard any unused portion. **Hypotension associated with Septic Shock** Dilute epinephrine in 5 percent dextrose solution or 5 percent dextrose and sodium chloride solution. These dextrose containing fluids provide protection against significant loss of potency by oxidation. Administration in saline solution alone is not recommended. Whole blood or plasma, if indicated to increase blood volume, should be administered separately. Add 1 mL (1 mg) of epinephrine from its Syringe to 1,000 mL of a 5 percent dextrose containing solution. Each mL of this dilution contains 1 mcg of epinephrine. Correct blood volume depletion as fully as possible before any vasopressor is administered. When, as an emergency measure, intraaortic pressures must be maintained to prevent cerebral or coronary artery ischemia, epinephrine can be administered before and concurrently with blood volume replacement.

	Whenever possible, give infusions of epinephrine into a large vein. Avoid using a catheter tie-in technique, because the obstruction to blood flow around the tubing may cause stasis and increased local concentration of the drug. Occlusive vascular diseases (for example, atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease) are more likely to occur in the lower than in the upper extremity; therefore, avoid the veins of the leg in elderly patients or in those suffering from such disorders. There is potential for gangrene in a lower extremity when infusions of catecholamine are given in an ankle vein. To provide hemodynamic support in septic shock associated hypotension in adult patients, the suggested dosing infusion rate of intravenously administered epinephrine is 0.05 mcg/kg/min to 2 mcg/kg/min, and is titrated to achieve a desired mean arterial pressure (MAP). The dosage may be adjusted periodically, such as every 10 to 15 minutes, in increments of 0.05 mcg/kg/min to 0.2 mcg/kg/min, to achieve the desired blood pressure goal. Continuous epinephrine infusion is generally required over several hours or days until the patient's hemodynamic status improves. The duration of perfusion or total cumulative dose cannot be predicted. After hemodynamic stabilization, wean incrementally over time, such as by decreasing doses of epinephrine every 30 minutes over a 12- to 24-hour period.
How Supplied	(b) (4) NDC 54288-117-10 (b) (4)
Storage	Epinephrine is light sensitive. Protect from light until ready to use. Do not refrigerate. Protect from freezing. Store at room temperature, between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.) Protect from alkalis and oxidizing agents. Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.
Container Closure [proposed]	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 24, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, 'NDA 205029' and 'epinephrine'. Our search identified 9 previous reviews[a,b,c,d,e,f,g,h,i], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Straka, Maximilian. Label and Labeling Review for Epinephrine Injection (NDA 205029/S-008). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 10. OSE RCM No.: 2020-2751.

[b] Straka, Maximilian. Review of Revised Label and Labeling Epinephrine Injection (NDA 205029/S-008). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 09. OSE RCM No.: 2020-2751-1.

[c] Straka, Maximilian. Label and Labeling Review for Epinephrine Injection (NDA 205029/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 30. OSE RCM No.: 2021-381.

[d] Straka, Maximilian. Review of Revised Label and Labeling Epinephrine Injection (NDA 205029/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 19. OSE RCM No.: 2021-381-1.

[e] Straka, Maximilian. Label and Labeling Review for Epinephrine Injection (NDA 205029/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 23. OSE RCM No.: 2021-604.

[f] Straka, Maximilian. Review of Revised Label and Labeling Epinephrine Injection (NDA 205029/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 JUL 16. OSE RCM No.: 2021-604-1.

[g] Straka, Maximilian. Label and Labeling Review for Epinephrine Injection (NDA 205029/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 AUG 24. OSE RCM No.: 2021-1404.

[h] Straka, Maximilian. Review of Revised Label and Labeling Epinephrine Injection (NDA 205029/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 SEP 21. OSE RCM No.: 2021-1404-1.

[i] Kane, Devin. Label and Labeling Review for Epinephrine Injection (NDA 205029/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JAN 13. OSE RCM No.: 2022-85.

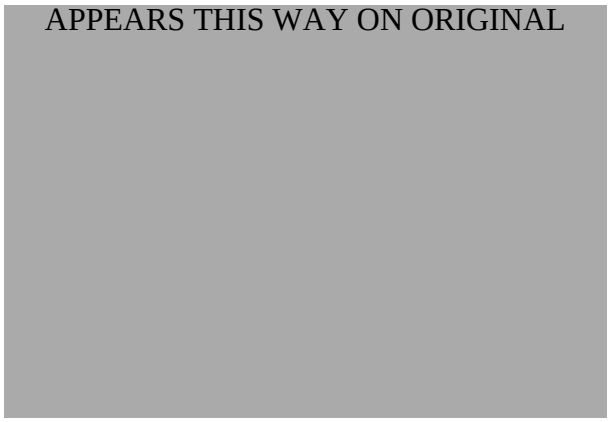
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error data, we reviewed the following Epinephrine Injection labels and labeling submitted by BPI Labs, LLC.

- Container label received on 04/03/2023
- Carton labeling received on 04/03/2023
- Prescribing Information (Image not shown) received on 04/03/2023, available from \\CDSESUB1\EVSPROD\nda205029\0104\m1\us\m1-14-labeling\m1-14-1-draft-labeling\m11413\draft-labeling-text-pdf.pdf

G.2 Label and Labeling Images



[j] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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04/14/2023 10:57:53 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	July 16, 2021
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ)
Application Type and Number:	NDA 205029/S-010
Product Name and Strength:	Epinephrine Injection, USP 1 mg/mL
Applicant/Sponsor Name:	Belcher Pharmaceuticals, LLC.
OSE RCM #:	2021-604-1
DMEPA 2 Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton and container labels received on July 1, 2021 for Epinephrine Injection, USP. We reviewed the revised carton labeling and container labels to determine if they are 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

We note the orientation of the barcode in the horizontal position and Belcher stated "considering the syringe in its horizontal position, the label also is designed to place on syringe in horizontal position such that the bar code could be scanned properly. We find the proposed labels and labeling acceptable from a medication error standpoint and we have no additional recommendations at this time.

[a] Straka, M. Label and Labeling Review for Epinephrine (NDA 205029/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 23. RCM No.: 2021-604

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LABEL & LABELING AND USE-RELATED RISK ANALYSIS 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:	June 23, 2021
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ)
Application Type and Number:	NDA 205029/S-010
Product Name, Dosage Form, and Strength:	Epinephrine Injection, USP 1 mg/mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Belcher Pharmaceuticals, LLC.
FDA Received Date:	March 19, 2021
OSE RCM #:	2021-604
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Belcher Pharmaceuticals, LLC. submitted a Prior Approval Supplement under NDA 205029 S-010 proposing a new pre-filled syringe (PFS) presentation of Epinephrine Injection, USP 1 mg/mL. The pre-filled syringe presentation is being proposed (b) (4) to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock via intravenous infusion.

We reviewed the proposed Epinephrine Injection, USP prescribing information (PI), container label and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Epinephrine Injection USP, approved on July 29, 2014 is a non-selective alpha and beta adrenergic agonist currently indicated:

- To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.
- For emergency treatment of allergic reactions (Type 1), including anaphylaxis (approved on April 11, 2016).
- For induction and maintenance of mydriasis during intraocular surgery (approved on October 23, 2015).

It is currently available as a single-use 1 mg/mL ampule, for intravenous, intramuscular, subcutaneous, and intraocular use.

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 Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Use-Related Risk Analysis (URRA)	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Belcher Pharmaceuticals, LLC. submitted a Prior Approval Supplement proposing a new pre-filled Syringe (PFS) presentation of Epinephrine Injection, USP 1 mg/mL. The pre-filled syringe presentation is (b) (4) for the indication to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock via intravenous infusion after dilution.

We note currently there is an approved Epinephrine Injection, USP in a PFS presentation available as a 1 mg/10 mL (0.1 mg/mL) Abboject Syringe. Belcher Pharmaceuticals is proposing (b) (4) (b) (4) On March 19, 2021 we sent Belcher Pharmaceuticals an Information Request (IR) requesting a comprehensive risk analysis and justification for not conducting a Human Factors (HF) study. Belcher Pharmaceuticals submitted a response on May 12, 2021 with the use-related risk analysis (URRA) and comparative analysis.

3.1 RISK BENEFIT ANALYSIS & CRITICAL TASKS COMPARISON

Belcher Pharmaceuticals, LLC. submitted a URRA and critical tasks comparison to support the claim that the overall benefit of supplying Epinephrine Injection, USP in a PFS outweighs the residual risks associated with potential identified failure modes. The Belcher Pharmaceuticals, LLC. prefilled syringe design is comparable to similar Luer Lock prefilled syringes on the market as FDA approved products whose usability are well established, therefore the proposed product design is not new and introduces no new risks. The Applicant analyzed the risks associated with the critical tasks in comparison between the proposed product, and three other Luer Lock prefilled syringes on the market. From this comparison, they determined that the residual risks are acceptable.

We note the currently marketed Epinephrine Injection, USP Abboject Syringe is approved for the same indication and route of administration as the proposed PFS. Both products require dilution prior to intravenous infusion. We have not identified errors related to the Abboject Syringe through our routine post marketing surveillance.

We reviewed the risk-benefit analysis and critical tasks comparison for the proposed pre-filled syringe product and agree that the residual risks are acceptable.

We reviewed the proposed Epinephrine Injection, USP prescribing information (PI), container label and carton labeling for areas of vulnerability that may lead to medication errors. We note that the package type term on the container label and carton labeling is (b) (4) and (b) (4) The container label has a linear barcode which can impede scanning due to the curvature of the syringe. The container label (b) (4) (b) (4) which can lead to improper (b) (4)

We determined that the PI, container label, and carton labeling can be improved from a medication error perspective. The PI lacks clarity and readability of the strength, dilution solution, and storage information and package type term is inconsistency. The term (b) (4) (b) (4) should be revised to “Single-Dose Syringe” and should be incorporated throughout the

PI. The carton labeling should emphasize the single intravenous route of administration to prevent accidental administration by other routes.

We provide recommendations in section 4.1 for the Office of Pharmaceutical Quality (OPQ) and in 4.2 for Belcher Pharmaceuticals LLC.

4 CONCLUSION & RECOMMENDATIONS

We agree with Belcher Pharmaceuticals' conclusion, that the overall benefit of supplying Epinephrine Injection, USP in a PFS outweighs the residual risks associated with potential identified failure modes. Additionally, we conclude that a HF validation study does not need to be submitted for their proposed product, Epinephrine Injection 1 mg/mL pre-filled syringe.

DMEPA concludes that the proposed PI, container labels, carton labeling can be improved from a medication error perspective. We provide recommendations in section 4.1 for the Office of Pharmaceutical Quality (OPQ) and in 4.2 for Belcher Pharmaceuticals LLC.

4.1 RECOMMENDATIONS FOR OFFICE OF PHARMACEUTICAL QUALITY (OPQ)

A. Highlights of Prescribing Information
   1. In Dosage and Administration, we recommend revising "dextrose solution" to the appropriate terminology. Revise to "5% Dextrose Injection, USP".
   2. In Dosage Forms and Strengths, the strength is presented as the (b) (4) (b) (4) We recommend revising the strength statement to include a (b) (4) for readability. Revise from (b) (4) to "1 mg per mL Syringe"
   3. We recommend revising the Dosage Forms and Strengths statement for consistency with the carton/container labeling. Revise (b) (4) to "single dose prefilled syringe".

B. Full Prescribing Information
   1. In Section 2.2, "Hypotension associated with Septic Shock", revise with the appropriate terminology per USP standards. Revise the term "5 percent dextrose solution" to "5% Dextrose Injection, USP".
   2. In Section 3 and Section 16, we recommend revising the Dosage Forms and Strengths statement for consistency with the carton/container labeling. Revise (b) (4) to "single dose pre-filled syringe".
   3. In How Supplied/Storage and Handling Section, the product supplied statement lacks clarity. We recommend revising the statement to (b) (4) (b) (4)

4.2 RECOMMENDATIONS FOR BELCHER PHARMACEUTICALS, LLC.

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

A. General Comments (Container labels & Carton Labeling)
   1. To improve readability, we recommend placing (b) (4) (b) (4) presentation. Revise (b) (4) to "1 mg/mL".

2. To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) on the container label and carton labeling to read "Recommended Dosage: See prescribing information."
3. The expiration date is not defined on the container labels or carton labeling. 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.
4. We recommend revising the statement [redacted] (b) (4) to "Single dose pre-filled syringe" for consistency with the prescribing information.

B. Container Labels

1. Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to syringe curvature.[a]
2. Revise the statement [redacted] (b) (4) to "For Intravenous Infusion ONLY" and increase the prominence to alert prescribers that this product can only be used intravenously.

C. Carton Labeling

1. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[b] 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.
2. Revise the statement [redacted] (b) (4) to "For Intravenous Infusion ONLY" and increase the prominence to alert prescribers that this product can only be used intravenously.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

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[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

[b] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Table 2 presents relevant product information for Epinephrine received on March 19, 2021 from Belcher Pharmaceuticals, LLC..

Table 2. Relevant Product Information for Epinephrine	
Initial Approval Date	July 29, 2014
Active Ingredient	Epinephrine
Indication	To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	1 mg/mL
Dose and Frequency	(b) (4)
How Supplied	
Storage	
Container Closure	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 19, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Epinephrine and NDA 205029. Our search identified four previous reviews[c,d,e,f], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Straka, M. Label and Labeling Review for Epinephrine (NDA 205029/S-008). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 10. RCM No.: 2020-2751.

[d] Straka, M. Label and Labeling Review Memo for Epinephrine (NDA 205029/S-008). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 9. RCM No.: 2020-2751-1.

[e] Straka, M. Label and Labeling Review for Epinephrine (NDA 205029/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 30. RCM No.: 2020-381.

[f] Straka, M. Label and Labeling Review Memo for Epinephrine (NDA 205029/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 19. RCM No.: 2020-381-1.

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Epinephrine labels and labeling submitted by Belcher Pharmaceuticals, LLC..

- Container label received on March 19, 2021
- Carton labeling received on March 19, 2021
- Prescribing Information (Image not shown) received on March 19, 2021, available from:
  - Clean: \\CDSESUB1\evsprod\nda205029\0067\m1\us\114-labeling\114a-draft-label\draft-labeling-text.pdf
  - Tracked: \\CDSESUB1\evsprod\nda205029\0067\m1\us\114-labeling\114a-draft-label\draft-labeling-text-tracked-changes.pdf

G.2 Label and Labeling Images

Container Label

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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