CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s000

SUMMARY REVIEW

Primary Medical and Cross-Discipline Team Leader Review

Date	17 July 2014
From	Shari L. Targum, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	#205029
Applicant	Belcher Pharmaceuticals
Date of Submission	29 January 2014
PDUFA Goal Date	29 July 2014
Proprietary Name / Established (USAN) names	Epinephrine injection, USP
Dosage forms / Strength	1 mg/mL 1:1000
Proposed Indication(s)	Increase mean arterial blood pressure in hypotension associated with septic shock.
Recommended:	*Approval pending DMEPA review and acceptance of label*

The DMEPA review of revised carton and container labels and insert labeling is pending at this time.

1. Introduction

The applicant has submitted a response to the Agency's Complete Response action for NDA #205029 (see Background, below). This review will address two outstanding issues from the original application review: CMC deficiencies and pediatric information.

2. Background

Epinephrine has been marketed for over 50 years. Epinephrine injection, USP auto-injector (each unit delivers 0.15 mg or 0.3 mg of epinephrine) is approved in the emergency treatment of severe allergic reactions (Type I). However, intravenous epinephrine, while marketed, is not approved for use in septic shock.

In 2006, the Agency began an initiative to remove unapproved drugs from the market and issued the guidance, "Marketed Unapproved Drugs—Compliance Policy Guide (CPG)." The applicant submitted NDA #205029 on December 4, 2012, for approval of epinephrine in septic shock, based on support from published literature [505(b) (2) submission].

However, CMC deficiencies in the review of NDA #205029 led to the issuance of a Complete Response (CR) action (4 October 2013). The applicant proposed a [redacted] However, the CMC review team did not agree and recommended that the product undergo [redacted] In addition, the CMC reviewers do not consider the proposed assays for drug and degradants to be adequately validated for use at release or on stability. (Establishment inspections were also incomplete).

The Agency also did not agree with the applicant's request for a full waiver of pediatric studies; the Agency instead requested that the applicant submit information from all available sources, including literature, in order to appropriately label epinephrine for the pediatric population.

3. CMC/Device

In the current review, the CMC reviewer has recommended approval for NDA 205029. The applicant has agreed to submit long-term storage stability data for three commercial batches for expiration dating extension of the drug product as a post-approval supplement.

- General product quality considerations

In this resubmission, the drug product formulation was revised [redacted] The CMC reviewer considered this [redacted] to be acceptable.

The proposed commercial manufacturing process entails [redacted] The drug product specification was revised for assay to [redacted] and included acceptance limits of no more than [redacted] and [redacted] for [redacted] at release and on stability respectively.

Stability data were provided for one batch of drug product manufactured with revised formulation and manufacturing process stored at long term storage conditions (25°C) up to 9 months. Based on the levels of [redacted] observed on stability, the applicant proposed a shelf-life of [redacted] months for the drug product. However, based on stability data showing that the drug product maintains the critical quality attributes up to 12 months, the CMC reviewer recommended a 12 month shelf-life for the drug product.

- Facilities review/inspection

The Office of Compliance has provided an overall acceptable recommendation for manufacturing and testing facilities for this NDA.

4. Nonclinical Pharmacology/Toxicology

In their review of the original application, the nonclinical pharmacology/toxicology reviewers found the NDA to be approvable; there are no new nonclinical pharmacology/toxicology data.

5. Clinical Pharmacology/Biopharmaceutics

In their review of the original application, the clinical pharmacology/biopharmaceutics reviewers recommended approval of epinephrine based on its effect on mean arterial pressure (MAP) in septic shock patients. The proposed dosing regimen in septic shock patients is 0.05 to 2.0 μg/kg/min continuous intravenous (IV) infusion titrated to achieve a target MAP.

A summary of key features from Dr. Hariharan's review:

- When administered intravenously, epinephrine rapidly disappears from plasma with an effective half-life of < 5 minutes. Time to pharmacokinetic steady state following continuous intravenous (IV) infusion is about 10 minutes.
- Following intravenous (IV) infusion, epinephrine has a quick onset of blood pressure response (< 5 minutes). The time to offset of effect is about 10-15 minutes.
- There is a trend for dose-dependent increase in blood pressure and heart rate with increasing doses of epinephrine (0.001 to 0.2 μg/kg/min) in healthy subjects.
- In septic shock patients, there is an increase in MAP with IV infusions of epinephrine. However, results of a naïve-pooled analysis suggest a high degree of inter-patient variability.
- Intrinsic factors such as age, body weight and disease severity may affect pharmacokinetics of epinephrine. However, due to the rapid onset and offset characteristics, close monitoring, and dose titration to a target response, no dose adjustments are warranted.

6. Clinical Microbiology

The microbiology reviewer recommended approval based on the original submission; there is no new microbiology information.

7. Clinical/Statistical- Efficacy

Dr. Moreschi recommended approval of epinephrine for the treatment of hypotension in septic shock. The basis of her approval recommendation was the consistent increase in mean arterial blood pressure supported by publication-based evidence. Dr. Moreschi had no recommendations for postmarketing requirements or commitments.

Dr. Bai concluded that the literature-based evidence was exploratory. I concur with Dr. Bai, but conclude that the consistent results in different publications over time support a role for epinephrine to increase mean arterial blood pressure in hypotensive patients with septic shock.

8. Safety

In reviewing the original application, Dr. Moreschi used the Twinject label, published literature provided by the sponsor, and references cited in Goodman and Gilman and Ellenhorn's Medical Toxicology to find case reports of the side effects from the use of epinephrine for longer periods of time.

In her review, Dr. Moreschi noted the high background mortality rate in septic shock and the resulting difficulty of calculating deaths from epinephrine use. She has also noted the lack of safety data with prolonged use of intravenous epinephrine. I concur. Intravenous pressors are routinely used in the intensive care unit, under close monitoring and telemetry. Moreover, intravenous epinephrine has a short half-life; thus, the drug can be stopped with rapid disappearance of plasma levels in the event of an adverse effect.

Epinephrine use was associated with palpitations (Illi 1995), tachycardia (Myburgh 2008), and cardiac arrhythmias (Mackie 1991, Brock 2003, Annane 2007) and metabolic effects such as lactic acidosis (Day 1996, Myburgh 2008), increase in blood sugar (Beck 1985) and increase in insulin requirement (Myburgh 2008).

Other events from published literature included: limb ischemia, stroke, myocardial ischemia and infarction, pulmonary edema, renal insufficiency. While these events could have been related to underlying conditions and/or concomitant medications, it is also plausible that these events resulted from epinephrine's pharmacologic effects and appropriate mention should appear in labeling.

9. Advisory Committee Meeting

This application was not presented to an advisory committee.

10. Pediatrics

In the Complete Response letter, the Agency requested that the applicant submit information from all available sources, including literature, to appropriately label this product for the pediatric population.

The applicant has submitted 5 published studies in infants and children, along with clinical practice guidelines for hemodynamic support of pediatric and neonatal septic shock from the American College of Critical Care Medicine (ACCM). A pharmacokinetic study in ill infants and children (Fisher 1993), some of whom had septic shock, revealed linear dose-proportional pharmacokinetics of epinephrine infusion that correspond with the pharmacokinetics observed in adult septic shock patients.

Table 1. Studies in pediatric patients provided by the applicant

Study	Design	Epinephrine dose	Duration of dosing	Results	Population/N exposed to epinephrine
Heckmann 2002	Retrospective chart review	0.05 to 2.6 µg/kg/min for first 24 hours	Median 17.25 (range: 3-124 hours)	↑ MABP +7 (-1 to 13) mm Hg, $p < 0.001$; ↑ HR +10 (-10 to 42) bpm, $p < 0.001$	Very low birth weight infants/31
Ceneviva 1998	Case series	0.13 ± 0.04 µg/kg/min (inotrope) or 0.48 ± 0.22 µg/kg/min (vasopressor)	Not stated	No results specific to epinephrine	Fluid-refractory septic shock/9 (vasopressor) + 9 (inotrope)
Han 2003	Retrospective cohort study	Not stated; epinephrine was included in treatment guidelines and not the primary intervention			Septic shock
De Oliveira 2008	Unblinded, randomized (ACCM/PALS guidelines with and without goal-directed therapy to achieve $ScvO_2^* \geq 70\%$)	Not stated; epinephrine was included in treatment guidelines and not the primary intervention			Severe sepsis or fluid-refractory septic shock
Brierley 2008	Unblinded observational study	Not stated; epinephrine was included in treatment guidelines			Fluid-resistant septic shock/12

*$ScvO_2$ = superior vena cava oxygen saturation

The applicant also referred to Fisher (1993) which evaluated pharmacokinetic data in six hemodynamically stable ill patients, 0.5 to 16 years-old, who were receiving an epinephrine intravenous infusion. I reviewed and discussed the Fisher publication with the clinical pharmacology reviewer (Dr. Sudarshan Hariharan); we did not find adequate pharmacodynamic data in the publication to guide instructions for use in pediatric patients.

Only one retrospective chart review (Heckmann) specifically mentions dosing and blood pressure results in one pediatric subgroup (e.g., very low birth weight infants). We are left with scant information regarding safety in pediatric patients. I therefore recommend that the applicant's proposed labeling in pediatric patients be modified to the standard language for "insufficient evidence." Accordingly, epinephrine should be approved for use in the adult population only.

The applicant made a "good faith" attempt to provide literature support for epinephrine use in pediatric patients. I also searched Pubmed (e.g., "epinephrine" "shock" "hypotension" "pediatric" "children") and could find no additional relevant publications. Based on previous literature searches of pressor use in pediatric patients with septic shock, I do not think that it will be easy, practical or feasible for the applicant to conduct a clinical trial of intravenous epinephrine use in this population. I therefore recommend that the applicant be granted a waiver from the requirement for pediatric studies.

11. Other Relevant Regulatory Issues

There were no DSI inspections or financial disclosures.

12. Labeling

- In a letter dated April 3, 2013, The Division of Medication Error Prevention and Analysis (DMEPA) concluded that the applicant's proposed proprietary name, (b) (4) was unacceptable due to (b) (4) The applicant's alternate proprietary name, (b) (4)
- In the current submission, the applicant has submitted carton and container and labeling for Epinephrine Injection, USP, without a proprietary name.
- In their May 28, 2014 review of the proposed container label, carton, and insert labeling, DMEPA made several recommendations to improve the proposed container label and carton labeling to increase the readability and prominence of important information on the label and labeling. The applicant revised the carton and container labels and DMEPA's review is currently pending.
- Labeling will be revised to reflect additional adverse events reported in the literature.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Pending acceptance of the revised carton and container labels and labeling, I recommend approval of epinephrine to increase mean arterial blood pressure in adult patients with septic shock.

The available literature appears insufficient to support efficacy and safety and provide guidance for dosing in pediatric patients. I think that it would be challenging for the applicant to conduct a randomized controlled clinical trial of epinephrine in this population. I therefore recommend that the sponsor be granted a waiver from the requirement for pediatric studies.

- Risk Benefit Assessment

The main benefit of epinephrine lies in its ability to increase mean arterial blood pressure and thereby maintain hemodynamic stability and adequate tissue perfusion in hypotensive patients with septic shock. Known risks of epinephrine appear to be related to its pharmacologic activity (e.g., hypertension, arrhythmias, tachycardia, hyperglycemia). Providers could monitor for these risks as intravenous pressors are routinely administered in intensive care units.

- Recommendation for other Postmarketing Requirements and Commitments:

None other than the stability study as agreed to by the applicant and CMC reviewers.

- Recommended Comments to Applicant:

Revised labeling should be sent to the applicant.

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/s/

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07/17/2014