CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA number	205029
Submission type	Standard 505(b)(2)
Submission date	12/04/2012
Applicant name	Belcher Pharmaceuticals, LLC
Proposed brand name	(b) (4)
Generic name	Epinephrine, USP
Dosage form	Sterile solution for injection (1 mL ampule)
Dosage strengths	1 mg/mL
Proposed indication	To increase systemic arterial blood pressure in acute hypotensive states associated with septic shock
OCP division	Division of Clinical Pharmacology 1
OND division	Division of Cardiovascular and Renal Products
Primary reviewer	Sudharshan Hariharan, Ph.D.
Team leader	Rajanikanth Madabushi, Ph.D.

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1. EXECUTIVE SUMMARY

Belcher Pharmaceuticals, LLC is seeking approval of Epinephrine, USP [1 mg/mL, 1 mL ampule] via the 505(b)(2) pathway for increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock. The proposed dosing regimen in septic shock patients is 0.05 to 2.0 µg/kg/min administered as continuous *i.v.* infusion titrated closely to achieve a target mean arterial pressure (MAP). The sponsor is relying on the safety information from Twinject [NDA 020800, approved May 2003] as the listed drug, an auto-injector approved for use in the emergency treatment of severe Type I allergic reactions. The sponsor relies on the published literature to support the non-clinical, clinical pharmacology and clinical efficacy of the proposed drug product. A literature based 505(b)(2) submission for epinephrine in support of the proposed indication was agreed upon by the Division of Cardiovascular and Renal Products during the pre-IND and pre-NDA meetings held on 02/03/2012 and 07/25/2012, respectively.

The clinical pharmacology package for this application primarily consists of published literature addressing the following topics – (i) pharmacokinetics (PK), (ii) pharmacodynamics (PD), (iii) dose-response in healthy and target population, and (iv) impact of intrinsic and extrinsic factors on PK and PD of epinephrine.

1.1. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The key clinical pharmacology features of epinephrine are summarized below:

- When administered intravenously, epinephrine rapidly disappears from the plasma with an effective half-life of <5 min. Time to reach pharmacokinetic steady state following continuous *i.v.* infusion is approximately 10 min.

- Following *i.v.* infusion, epinephrine has a quick onset of blood pressure response (<5 min). The time to offset the drug effect is approximately 10-15 min.

- 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 mean arterial pressure with *i.v.* infusions of epinephrine. However, a naïve-pooled analysis shows a similar change from baseline MAP response over a wide range of epinephrine infusion rates suggesting a high degree of inter-patient variability.

- Intrinsic factors such as age, body weight and disease severity may affect the pharmacokinetics of epinephrine. However, due to quick onset and offset of effect, dose-adjustment based on exposure changes is not necessary as epinephrine is to be administered in a controlled clinical setting titrated to a target response. Similarly, drug interactions affecting the PK or PD of epinephrine also does not warrant any dose adjustment.

1.2. Phase 4 Requirements / Commitments

No Phase 4 Requirements / Commitments are proposed at this point of time.

1.3. Recommendation

The Office of Clinical Pharmacology (OCP/DCP1) recommends approval of epinephrine based on its effect on MAP in septic shock patients.

2. QUESTION BASED REVIEW

An abridged version of the question based review is used to address specific clinical pharmacology issues of epinephrine related to this submission. Review of individual publications pertaining to the clinical pharmacology aspects of epinephrine can be found in the Appendix.

2.1. What are the disposition characteristics of epinephrine?

Epinephrine is rapidly cleared from the plasma following an *i.v.* administration with an effective half-life of <5 min. A pharmacokinetic steady state following continuous *i.v.* infusion is achieved within 10-15 min. Epinephrine is not effective after oral administration because it is rapidly conjugated and oxidized in the gastrointestinal mucosa and liver. Absorption from subcutaneous tissues occurs relatively slowly because of local vasoconstriction and the rate may be further decreased due to systemic hypotension in cases such as septic shock. Following an intramuscular injection, absorption is relatively rapid, however, in emergencies such as septic shock, it is necessary to administer epinephrine intravenously. Pharmacokinetics of epinephrine is dose proportional in the infusion dose range of 0.026 to 1.67 µg/kg/min in the target population i.e., septic shock [Fig. 1].

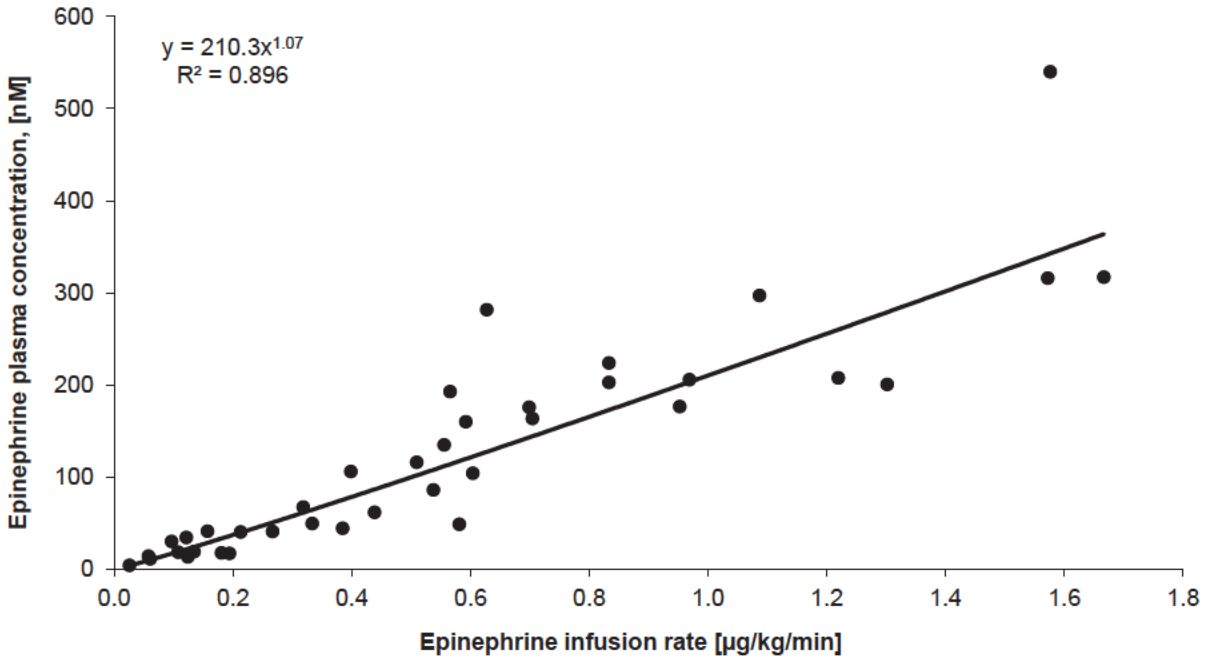

Figure 1: Epinephrine plasma concentration as a function of infusion rate at steady state showing dose linearity in the range 0.026 to 1.67 µg/kg/min.

Epinephrine is extensively metabolized with only a small amount being excreted unchanged. Both endogenous and exogenous epinephrine is preferentially metabolized by catechol-*O*-methyl transferase [COMT] in extraneuronal pathways, with less epinephrine being deaminated by monoamine oxidase [MAO]. COMT and MAO are abundantly expressed in the liver, kidneys

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