CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s000

MEDICAL REVIEW(S)

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS

Divisional Memo

NDA: 205029 Epinephrine injection for raising blood pressure in the hypotension associated with septic shock.

Sponsor: Belcher Pharmaceuticals

Review date: 25 April 2014

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo conveys the Division's recommendation to issue an Approval letter for this application.

This application was previously the subject of a Complete Response (4 October 2014). The resubmission (29 January 2014) has been the subject of reviews of CMC (Bhamidipati; 14 July 2014) and DMEPA (Stewart; 16 July 2014). There is a comprehensive CDTL memo (Targum; 17 July 2014) with which I am in full agreement. I highlight a few matters here.

Numerous CMC issues raised in the CR letter were all satisfactorily addressed. However, the agreed-upon shelf life of 12 months is supported by data from only one commercial batch. The sponsor commits to providing data from 3 commercial batches post-marketing.

Numerous recommendations on carton and container labeling were addressed. There are no remaining issues.

The only other deficiency noted in the CR letter pertained to pediatric data. The sponsor addressed the issue with a literature review. Dr. Targum reviewed these materials and did not find additional references upon her independent literature search. Dr. Targum concludes, and I concur, that the sparse literature does not provide adequate information about the effectiveness and safety of epinephrine to raise blood pressure in children with sepsis. The sponsor, Dr. Targum, and I concur that study of epinephrine for this use is highly impractical, given the incidence, so we will waive the PREA requirement for further study.

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/s/

NORMAN L STOCKBRIDGE
07/25/2014

Cross-Discipline Team Leader Review

Date	28 September 2013
From	Norman Stockbridge
Subject	Cross-Discipline Team Leader Review/ Division Director memo
NDA/BLA # **Supplement#**	205029 000
Applicant	Belcher Pharmaceuticals
Date of Submission	4 December 2012
PDUFA Goal Date	4 October 2013
Proprietary Name / Established (USAN) names	(b) (4) (DMEPA approved 7 August 2013) Epinephrine
Dosage forms / Strength	Intravenous solution 1 mg/mL
Proposed Indication(s)	1. Pressor in patients with septic shock
Action:	Complete response

1. Introduction

Epinephrine has been marketed for over 50 years. This would be its first approval as a pressor, although it is approved to treat anaphylaxis and induction and maintenance of mydriasis during intraocular surgery.

2. Background

The application is literature-based.

3. CMC/Device

I refer to the CMC review by Dr. Bhamidipati (21 August 2013). There are no issues with regard to drug substance or drug product, and stability data support a (b) (4) The sponsor seeks a (b) (4) The CMC team does not agree with this and recommends that the product be (b) (4)

The CMC team does not consider the proposed assays for drug and degradants to be adequately validated for use at release or on stability.

Establishment inspections are currently incomplete.

The CMC deficiencies are the sole bases for a Complete Response.

4. Nonclinical Pharmacology/Toxicology

I refer to Dr. Dwivedi's review (19 June 2013). Epinephrine is a fairly non-selective systemic vasoconstrictor, raising blood pressure in septic shock or other vasodilatory states. At some point, mesenteric, renal, and coronary circulations are compromised. Pulmonary resistance seems relatively unaffected.

Metabolic effects include hypokalemia and hyperglycemia. The latter of these leads to increased lactic acid as metabolism shifts more aerobic. The effect does not appear to reflect hypoxia; oxygen utilization generally increases slightly.

Epinephrine leads to impaired implantation and increased fetal loss in rabbits, supporting pregnancy class C labeling.

5. Clinical Pharmacology/Biopharmaceutics

I refer to the review by Dr. Hariharan (9 September 2013). The effective half-life of epinephrine is about 5 minutes. The pressor effect has little or no latency. There is enormous between-subject variability in response, probably reflecting various vasoconstrictive influences. This variability supports the proposed dose range of 0.05 to 2 mcg/kg/min.

6. Clinical Microbiology

I refer to Dr. Donald's review (15 February 2013). The sponsor's (b) (4) procedure was considered adequate from a microbiological point of view. By personal communication, the microbiology team supports the decision to have the sponsor switch to (b) (4)

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