CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	205029
Drug Name:	Epinephrine Injection, USP 1:1000 (mg/mL)
Indication(s):	increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock
Applicant:	Belcher Pharmaceuticals, LLC
Date(s):	11/30/2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Steve Bai, Ph.D.
Concurring Reviewers:	James Hung, Ph.D. Director DBI
Medical Division:	Division of Cardiovascular and Renal Products
Clinical Team:	Gail Moreschi, MD
Project Manager:	Russell Fortney

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Belcher did not conduct any clinical studies to assess the potential benefit of Epinephrine Injection USP, 1:1000 (1 mg/mL) in the aspects of the artial blood pressure. In-stead, Belcher relied on the established safety on the listed drug Twinject and the published literature. The clinical studies identified from the published literature seem to suggest that Epinephrine may have an effect to increase the arterial blood pressure, measured by MAP, in patients with septic shock. Although a large body of published literature is available, these studies do not rise to the level to be able to provide evidence for concluding the effectiveness of Epinephrine in increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock.

2 INTRODUCTION

2.1 Overview

Belcher submitted this 505(b) (2) application for Epinephrine Injection USP, 1:1000 (1mg/mL). The proposed indication is for use in increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock. This submission relies on published literature to support the efficacy of Epinephrine. Belcher is relying on safety information from Twinject (NDA 20800). Twinject is an approved Epinephrine (0.3 mg/mL) product for use in the emergency treatment of severe allergic reactions (Type I).

No clinical studies of Belcher's Epinephrine Injection USP, 1:1000 (1 mg/mL) have been conducted. The Agency agreed that a literature-only NDA submission was acceptable on an End of Phase I meeting held on 25 July, 2012. The published literature was searched for clinical studies of epinephrine used in the treatment of shock. A search of PubMed, using the terms epinephrine (adrenaline), hypotension, infusion, shock, sepsis, septic shock, human, patients, study, and/or clinical trial was performed. Searching all fields for "(septic shock)", "(blood pressure)", "infusion", "hypotension", and "(epinephrine or adrenaline)" led to 33 results. From these studies, articles relevant to epinephrine's use in hemodynamic support were reviewed, and 14 key articles (emphasizing randomized, controlled studies comparing intravenous epinephrine to alternative treatments) were selected to be summarized.

The Septic Shock (SS) in adults refers to a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Septic shock is a severe form of sepsis with arterial hypotension despite adequate body fluid resuscitation (replacement). Furthermore, the sepsis is the clinical syndrome defined by the presence of both infection and a systemic inflammatory response (SIRS), and more specifically, SIRS in response to infection. The Septic shock accounts for about 9% of admissions to intensive care units, and its short-term mortality ranges between 40% and 60%.

Vasopressor is an intriguing hormone in that it has little vasoconstrictor effect in hemodynamically normal subjects, but is an important pressor in states where arterial pressure is threatened. It has been used in prevention and management of vasodilatory shock, as an alternative of catecholamine pressors. Intravenous Epinephrine has been used as a vasopressor

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