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.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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)

7. Clinical/Statistical- Efficacy

I refer to reviews by Drs. Bai (statistical; 9 September 2013) and Moreschi (clinical; 19 September 2013). The literature supporting approval comes from many small studies over many years. Dr. Bai calls them "exploratory", but they tell a consistent story of epinephrine's not very subtle hemodynamic effects.

The Bollaert (1990) results are typical. Thirteen subjects with dopamine-resistant sepsis-related hypotension underwent uncontrolled treatment with epinephrine 0.5 or 1 mcg/kg/min and right heart catheterization at about 1 h. Systolic pressure increased from a mean of 73 to a mean of 120 mmHg and cardiac index increased from about 5.5 to about 6.7 L/min/m^2. Systemic vascular resistance increased by about 20%, but pulmonary vascular resistance was unchanged. VO_2 increased by about 10%. Mortality was greater than 50%.

Similar results are seen in many other studies reviewed by Dr. Moreschi, with doses ranging from 0.025 to 18 mcg/kg/min and administered for a week or more.

8. Safety

The safety database is little better than anecdotal. Invasive monitoring is routine, with the goal of optimizing perfusion of critical organs. Epinephrine does not appear to be proarrhythmic.

9. Advisory Committee Meeting

None.

10. Pediatrics

The PeRC recommended that the Division advise the sponsor that its pediatric plan is deficient and ask the sponsor to submit information from all available sources, including literature, to appropriately label the product for the pediatric population. I concur.

11. Other Relevant Regulatory Issues

DSI inspected nothing.

Financial disclosure information was not available, but none of the cited studies was sponsored by Belcher.

12. Labeling

Labeling will look similar to that of other recently approved agents for vasodilatory shock. Dr. Moreschi cites published guidelines that suggest that epinephrine be used after norepinephrine or dopamine, but neither the authors nor Dr. Moreschi finds the data persuasive for calling epinephrine second-line.

13. Recommendations/Risk Benefit Assessment

But for CMC issues, epinephrine is approvable to increase the blood pressure in the setting of septic shock.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
09/28/2013

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	205-029
Priority or Standard	Standard
Submit Date(s)	November 30, 2012
Received Date(s)	December 4, 2012
PDUFA Goal Date	October 4, 2013
Division / Office	DCRP/OND I
Reviewer Name(s)	Gail Moreschi, MD, MPH
Review Completion Date	September 19, 2013
Established Name	Epinephrine (HCL) Injection
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Sympathomimetic (adrenergic)
Applicant	Belcher Pharmaceuticals, LLC
Formulation(s)	1:1000 (1 mg/mL)
Dosing Regimen	IV
Indication(s)	Increase Blood Pressure
Intended Population(s)	Hypotensive States with Septic Shock

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Epinephrine has been utilized worldwide for many years as a pressor in hypotensive states. Studies from the literature document and confirm epinephrine's efficacy in the treatment of hypotension. The literature however is incomplete as to all the possible adverse events that can occur with the use of epinephrine in septic shock during the hours or days that it might be utilized. By knowing the pharmacology of epinephrine it is possible to address these potential side effects. Patients treated for septic shock must be closely monitored for cardiac, vascular, respiratory, and metabolic events. Epinephrine should be approved for treatment of hypotension in septic shock.

1.2 Risk Benefit Assessment

Septic shock is a very serious illness necessitating fluids and antibiotics in addition to the treatment of hypotension. Epinephrine is valuable in the treatment of this serious often fatal illness.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

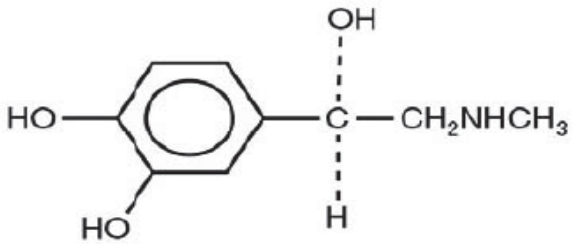
2 Introduction and Regulatory Background

In June 2006, the Agency announced a new drug safety initiative to remove unapproved drugs from the market, including a final guidance entitled "Marketed Unapproved Drugs - Compliance Policy Guide (CPG)." Epinephrine has been utilized for years for the treatment of hypotension associated with septic shock. Epinephrine for intravenous use for the treatment of hypotension has not yet received FDA approval.

2.1 Product Information

Epinephrine (Adrenaline) is a sympathomimetic (adrenergic) agent. Its structural formula is presented in the following figure.

Figure 1: Structure of epinephrine



2.2 Currently Available Treatments for Proposed Indications

Both dopamine and norepinephrine have been approved by the FDA in the treatment of septicemia. Dopamine hydrochloride was originally approved as Intropin in 1974 and is currently available generically for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Norepinephrine bitartrate was originally approved in 1950 as Levophed for blood pressure control in certain acute hypotensive states (e.g., pheochromocytomectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions).

Recently, 20 December 2012, phenylephrine hydrochloride was approved for the treatment of vasodilatory shock, including septic shock.

2.3 Availability of Proposed Active Ingredient in the United States

There are several unapproved and more than 39 approved drug formulations containing epinephrine currently marketed. Epinephrine injection is currently available in 1 mg/mL, (1:1000), 0.1 mg/mL (1:10,000), and 0.5 mg/mL (1:2,000) solutions.

2.4 Important Safety Issues With Consideration to Related Drugs

The Surviving Sepsis Campaign program of 2008 has recommended norepinephrine and dopamine to be the initial vasopressors of choice for maintaining a mean arterial pressure (MAP) of at least 65 mmHg in septic shock patients with epinephrine as the alternative vasopressor when there is a poor response to norepinephrine or dopamine. However, this Campaign admits there is not enough evidence to recommend one vasopressor over another.

Dopamine increases the mean arterial pressure and the cardiac output due to an increase in stroke volume and heart rate, but has a minimal effect on the systemic vascular resistance. Therefore dopamine fails to increase the MAP when systemic vascular resistance is low (**Levy 2005c**). Dopamine causes more tachycardia and maybe more arrhythmogenic than epinephrine. Additionally dopamine may influence the endocrine response via the hypothalamicpituitary axis and may have immunosuppressive effects.

Compared with dopamine, norepinephrine increases mean arterial pressure due to its vasoconstrictive effects and has little change in heart rate and less of an increase in stroke volume. Other side effects may be similar to epinephrine.

Phenylephrine can cause angina, tissue necrosis, allergic reactions, peripheral and visceral vasoconstriction, and the need for renal replacement therapy.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sponsor submitted a Pre-IND (b) (4) on (b) (4) for epinephrine to be used (b) (4) The FDA responded stating that increasing the blood pressure in patients in shock may serve as a basis for approval. On 3 February 2012 in a teleconference the sponsor informed the FDA that they were interested in pursuing the indication of increasing blood pressure in certain hypotensive states. The FDA agreed that this may be an appropriate indication.

On 25 July 2012 the sponsor met with the FDA for an End-of Phase 1 (EOP1) meeting. The Agency stated that a literature only NDA for epinephrine to increase the blood pressure in patients with septic shock was acceptable provided that the sponsor note and consider the limitations in the assay methodology in the published PK and PD studies for epinephrine.

On 18 September 2012 the sponsor submitted questions to the Agency which were answered by the FDA regarding the clinical pharmacology studies.

2.6 Other Relevant Background Information

Intravenous epinephrine has been used as a vasopressor for over 50 years in treating hypotension associated with septic shock. Both the published clinical studies and the algorithms of numerous medical organizations around the world recommend epinephrine for the management of hemodynamic support.

3 Ethics and Good Clinical Practices

Since this is a literature-based application, this reviewer has no access to raw data or site inspections and cannot, therefore, make any assertion regarding the integrity of an individual trial cited in this review. There are no financial disclosures to review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemistry review by Shastri Bhamidipati, Ph.D., is not recommending approval due to significant issues in regards to the quality of the drug product resulting from the proposed commercial manufacturing process. Please refer to his review for a detailed account.

4.2 Clinical Microbiology

No product quality microbiology deficiencies were identified based upon the information provided. NDA 205029 is recommended for approval.

4.3 Preclinical Pharmacology/Toxicology

Rama S. Dwivedi, Ph.D., states in his review that epinephrine is approvable. Additionally he has the following comments:

“Results from nonclinical septic model studies have shown that administration of epinephrine has significantly improved the mean arterial pressure (MAP) and myocardial performance in a dose dependent manner, by increasing contractility, stroke volume, and cardiac output. However, nonclinical data are limited in reproducing the severe sepsis seen in humans.

Metabolic effects such as hyperlactemia, hyperglycemia and hypokalemia, decreased mesenteric, coronary and renal conductance were associated with epinephrine treatment (Levy 2003)."

"The data from published reports suggest that epinephrine was not carcinogenic in 2-year rat studies."

"Epinephrine has been shown to interfere with ovum implantation and fetus survival in rabbits (Auletta, 1971)."

"In addition to this, implantation loss, incidence of arrested fetuses and gastroschisis were observed in epinephrine-treated Dutch-Belted rabbits, showing a teratogenic potential of epinephrine."

4.4 Clinical Pharmacology

In a draft review by Sudharshan Hariharan, Ph.D., "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 in the range of 10 min.

- Epinephrine has a rapid onset and offset of blood pressure effect.

- There is a trend for dose-dependent increase in blood pressure and heart rate with increasing doses of epinephrine in healthy subjects. However, the experience is relatively at the lower dose range [0.001 to 0.2 µg/kg/min] when compared to the proposed dosing regimen [0.05 to 2.0 µg/kg/min] in septic shock patients.

- In septic shock patients, there is an increase in mean arterial pressure with intravenous infusions of epinephrine. However, from a naïve-pooled analysis there is no trend for a relationship between epinephrine dose and mean change from baseline due to high inter-patient variability in response.

- Intrinsic factors such as age, body weight and disease severity may affect the pharmacokinetics of epinephrine. However, 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. For similar reasons, drug interactions affecting the pharmacokinetics or pharmacodynamics of epinephrine also do not warrant any dose adjustment."

5 Sources of Clinical Data

The entire clinical submission was a literature review.

5.1 Tables of Studies/Clinical Trials

NA

5.2 Review Strategy

No clinical studies were completed and submitted by the sponsor. The sponsor submitted articles documenting the efficacy of epinephrine. However, the sponsor essentially used the label of Twinject, NDA 020800, for safety which has a different indication, the emergency treatment of severe allergic reactions (Type I), different dose, and route of administration. Therefore, this reviewer looked for adverse effects from the longer use of epinephrine for hours and/or days. Essentially not much is published in the literature regarding the long term adverse effects of epinephrine.

5.3 Discussion of Individual Studies/Clinical Trials

These studies varied in their design, whether or not they were controlled studies and how long they observed and treated septic shock patients. Some studies even included shock from other causes.

6 Review of Efficacy

Efficacy Summary

The literature review submitted by the sponsor documents the efficacy of epinephrine in the treatment of hypotension from septic shock. This treatment has been used for years without FDA approval which they are seeking with this submission.

6.1 Indication

The indication the sponsor is seeking is for use in increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock. Currently there is no FDA approved intravenous epinephrine for hemodynamic stabilization in septic shock.

In 1991 the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) held a consensus conference to define the pathophysiology of sepsis. “Sepsis” is the clinical syndrome defined by the presence of both infection and a systemic inflammatory response in response to the infection. In the U.S more than 200,000 persons die annually from sepsis. "Septic shock" in adults refers to a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes.

In 2001 the signs and symptoms for sepsis were expanded to include hemodynamic instability, arterial hypoxemia, oliguria, coagulopathy and altered liver function tests. These signs and symptoms may be indicative of organ dysfunction.

Arterial hypotension is the main hemodynamic parameter of sepsis, and occurs when systolic blood pressure drops below 90 mmHg; when mean arterial pressure (MAP) drops below 70 mmHg; or when systolic blood pressure decreases more than 40 mmHg in adults or in children.

The treatment of septic shock includes many parameters but hypotension is extremely important. For a patient to survive this critical illness all the parameters must be treated. The studies involving the use of epinephrine for the treatment of hypotension in septic shock have developed historically and this historical time frame will be used in the following efficacy section. The sponsor has submitted 14 published studies in support of the efficacy of epinephrine for this indication. Many of these studies are small and most are redundant. Succinct information from each article will be provided as follows.

Bollaert 1990: Effects of epinephrine on hemodynamics and oxygen metabolism in dopamine-resistant septic shock

Design: A prospective study performed to assess the effects of epinephrine on hemodynamic and metabolic variables in 13 septic shock patients who remained hypotensive after both fluid loading and dopamine administration. It is noteworthy that the study measurements were taken for only 1 hour.

Treatment: A continuous infusion of epinephrine was started at a rate of 0.5 µg/kg/min. After 30 minutes, if systolic pressure was still below 90 mmHg, epinephrine was increased to 1 µg/kg/min. Before epinephrine treatment, patients had a systolic pressure under 90 mmHg, oliguria of less than 15 mL/hour, and a positive blood test for infection. All patients had mechanical ventilation and received broad-spectrum antibiotics without any steroids. Patients were enrolled if a dopamine infusion of greater than 15 µg/kg/min (15-30 µg/kg/min) failed to restore the systolic pressure above 90 mmHg. In 4 cases, dopamine was administered in addition to 10 µg/kg/min dobutamine. The ages of patients enrolled ranged from 15 to 74 years (only 1 patient was < 18 years).

Hemodynamic measurements were performed before and 1 hour after the start of epinephrine infusion. A short-term reversal of hypotension was achieved in all patients. Six patients were administered epinephrine at 0.5 µg/kg/min and 7 patients received epinephrine at 1 µg/kg/min. Hemodynamic changes are shown in the following table from the published study report.

Table 1: Hemodynamic and metabolic parameters in 13 dopamine-resistant patients at baseline and after 1 hour epinephrine infusion

COPYRIGHT MATERIAL WITHHELD

.Values are given as mean ± SD
†Data available for 12 patients
HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PWP = pulmonary wedge pressure; CI = cardiac index; SVI = stroke volume index; LVSWI = left ventricular stroke work index; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index; DO_2 = oxygen delivery; VO_2 = oxygen consumption; ER = extraction ratio; NS = not significant

Seven patients died of their septic episode. Among the 6 survivors, 5 were discharged from the hospital and 1 died 2 weeks later of another septic episode. The authors concluded that epinephrine is an appropriate alternative in dopamine-resistant patients and could be useful in the most severe septic shock states where fluid replacement and dopamine have failed. They also state that the hemodynamic and metabolic effects of epinephrine appear to be more predictable and more appropriate to the accepted goals of septic shock therapy than norepinephrine.

Mackenzie 1991: Epinephrine in treatment of septic shock: effects on hemodynamics and oxygen transport

Design: An open-label, single-group study in 13 patients (7 male, 6 female) with septic shock persisting after optimal fluid loading to assess the effects of epinephrine on hemodynamics and oxygen transport.

Treatment: Epinephrine was administered by intravenous infusion at an increasing dose, starting at a rate of 0.05 µg/kg/min and increased by increments of 0.05 µg/kg/min. Assessments for incremental dose adjustments were performed every 15 minutes. This protocol was followed until either the cardiac index exceeded 4.5 L/min/m^2 or the oxygen delivery index exceeded 600 mL/min/m^2; there was no further increase in cardiac index; dysrhythmias or other side effects became apparent; or a change in the management was judged appropriate on clinical grounds. The mean maximum epinephrine dose was 0.16 (0.05 to 0.42) µg/kg/min.

The ages of the patients enrolled ranged from 46 to 87 years. In these patients, there were significant increases in MAP, cardiac index, left ventricular stroke work index, and oxygen delivery index as shown in the table below from the published study. There was no significant change in oxygen consumption although the trend was toward an increase. There was a significant reduction in oxygen extraction ratio, but no change in shunt fraction.

Table 2: Hemodynamic and oxygen transport changes with epinephrine from baseline

	Baseline (Mean ± SEM)	Adrenaline (Mean ± SEM)	Significance
COPYRIGHT MATERIAL WITHHELD			

NS = not significant; PCWP = pulmonary capillary wedge pressure; MAP = mean arterial pressure; SVR = systemic vascular resistances; CI = cardiac index; DO2I = oxygen delivery index; VO2I = oxygen consumption index; OER = oxygen extraction ratio; Qs/Qt = shunt fraction; LVSWI = left ventricular stroke work index

The survival rate was 46% (7 of 13 patients died). The authors concluded that epinephrine had beneficial hemodynamic effects in septic shock by increasing MAP, cardiac index, and oxygen delivery.

Lipman 1991: Vasoconstrictor effects of epinephrine in human septic shock
Design: An open-label, single-group study in 10 patients with 11 episodes of septic shock To assess the hemodynamic effects (especially the vasoconstrictor effects) of epinephrine In septic shock.

Treatment: Epinephrine was given when systemic vascular resistance dropped below 600 dyn·s/cm^5 and was titrated to achieve a systemic vascular resistance of no higher than 800 dyn·s/cm^5. Epinephrine was used for an average of 7.3 days (range 2-19 days), and the maximum doses ranged from 0.11 to 0.47 µg/kg/min. Dopamine was kept constant throughout the study at 2 to 3 µg/kg/min for renal protection. In addition, dobutamine was used if cardiac index was < 4.5 L/min/m^2.

The ages of patients enrolled ranged from 35 to 72 years. The variables measured included mean blood pressure, pulmonary capillary wedge pressure, cardiac index, stroke volume index, systemic vascular resistance, left ventricular stroke work index, heart rate, and serum creatinine. Student's t-test was used to determine the significance of the difference between variables pre-epinephrine and on maximum epinephrine.

There was no reliable dose response curve of epinephrine. If high enough doses were given, the systemic vascular resistance eventually increased. There was no deterioration in cardiac index or further increase in pulse rate and no renal damage was demonstrated. The hemodynamic variables are presented in the following table from the published study.

Table 3: Hemodynamic variables prior to epinephrine administration, at maximum administration, and following administration

	Pre adrenaline	On maximum adrenaline	Post adrenaline
COPYRIGHT MATERIAL WITHHELD			

Five patients were discharged from the hospital. Three died still septic, 1 from septic shock, 1 from a technical fault still in septic shock, and 1 from an uncontrollable bowel sepsis but Not in shock. The survivors were on epinephrine for an average of 4.5 days (range 2-7 days) and nonsurvivors for an average of 10.8 days (range 3-19 days).

The authors concluded that epinephrine can be used as a vasoconstrictor in septic shock without adverse effects, but initial doses have to be high and the effects measured and titrated carefully. Used this way, the authors conclude that epinephrine provides time for the eradication of sepsis.

Wilson 1992: Septic shock: does adrenaline have a role as a first-line inotropic agent?
Design: A prospective study in 15 adult patients evaluating the effects of epinephrine on the hemodynamics and oxygen transport when used as a first-line inotropic agent in septic shock.

Treatment: Epinephrine was infused starting at 0.025 µg/kg/min and increased by 0.025 µg/kg/min every 20 minutes until a sustained increase of systolic blood pressure to at least 120 mmHg occurred, an increase in systemic vascular resistance of 200 $dyn.s.cm^{-5}$ above baseline, or an increase in the heart rate of above 20% of that initially recorded was obtained. The maximum epinephrine infusion rate ranged from 0.05 to 0.3 µg/kg/min. The authors noted a variable dose response between patients and therefore recommended close hemodynamic monitoring. The patients were treated after an adequate fluid loading, early in the septic insult and without other inotropic agents. However, some of the patients may have had low-dose dopamine before entering the trial.

The MAP increased significantly from baseline as shown in the table below from the published trial. The increase in blood pressure was partially due to an increase in cardiac index (23%) and systemic vascular resistance (16%). The left ventricular stroke work index increased by 70%. A small increase in heart rate occurred up to 8 bpm, but that was not found to be clinically significant. There was no significant change in pulmonary artery pressures and pulmonary vascular resistance, and the pulmonary capillary wedge pressure was kept constant as per design.

Table 4: Hemodynamic and oxygen transport variables

	Baseline	Max. dose	Difference	95% CI
COPYRIGHT MATERIAL WITHHELD				

The overall intensive care unit (ICU) mortality rate was 66% with an average admission Apache II score of 20. Of the 5 patients who survived, 4 showed no change or small decreases in lactate levels, whereas in the 8 patients who died and had lactate measured, all showed an increase in lactate levels. Overall, the authors concluded that epinephrine is an effective initial inotropic agent.

Moran 1993: Epinephrine as an inotropic agent in septic shock: a dose-profile analysis

Design: A prospective clinical study conducted to characterize the acute actions and physiologic dose profile of epinephrine as a single inotrope in 9 male and 9 female adult patients with septic shock.

In the dose range of 3 to 18 µg/min, epinephrine produced linear increases in average heart rate, MAP, cardiac index, left ventricular stroke work index, stroke volume index, and oxygen delivery and consumption as shown in the following table from the published study. No effect was noted for pulmonary artery occlusion pressure, mean pulmonary arterial pressure, or systemic vascular resistance index.

Table 5: Hemodynamic data and blood gas values at baseline and during epinephrine infusions

Dose (µg/min)	HR (beats/ min)	MAP (mm Hg)	RAP (mm Hg)	MPAP (mm Hg)	PAOP (mm Hg)	CI (L/min /m²)	SI (mL/ m²)
COPYRIGHT MATERIAL WITHHELD							

LVSWI (g·m/m²)	SVRI (dyne·sec/ cm⁵·m²)	Arterial pH	$\dot{V}O_2$ (mL/ min/m²)	$\dot{D}O_2$ (mL/ min/m²)	$\dot{Q}sp/\dot{Q}t$ (%)	O_2 Extr (%)
COPYRIGHT MATERIAL WITHHELD						

HR = heart rate; MAP = mean arterial pressure; RAP = right atrial pressure; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure; CI = cardiac index; SI = stroke volume index; LVSWI = left ventricular stroke work index; SVRI = systemic vascular resistance index; VO_2 = oxygen consumption; DO_2 = oxygen delivery; Qsp/Qt = shunt fraction; O_2 Extr = oxygen extraction ratio
p refers to the test of significance for zero slope in the equation E (variable) = a + b x dose, where E is the expected or predicted average value, a is the interrupt, and b is the slope of the line.

The overall mortality rate was 33%. Epinephrine infusions were well-tolerated with no clinically important ventricular or supraventricular dysrhythmias during the study. The authors concluded that epinephrine increases the oxygen delivery index in septic shock by increasing cardiac index without an effect on systemic vascular resistance index or pulmonary artery occlusion pressure.

Levy 1997: Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study

Design: A prospective, randomized clinical trial to compare the effects of norepinephrine and dobutamine (N = 15) to epinephrine (N = 15) on hemodynamics, lactate metabolism, and gastric tonometric variables in hyperdynamic dopamine-resistant septic shock.

Treatment: Epinephrine and norepinephrine infusions were started at 0.3 µg/kg/min and

increased using the MAP at 5-minute intervals to obtain an MAP above 80 mmHg after the first hour when dopamine was stopped. Dobutamine was infused at a fixed dose of 5 µg/kg/min in the norepinephrine group. Mean epinephrine doses were 0.45 µg/kg/min at hour 1, 0.52 µg/kg/min at hour 6, 0.48 µg/kg/min at hour 12, and 0.36 µg/kg/min at hour 24. At hours 1, 6, 12, and 24, the infusion rates of norepinephrine were 0.44, 0.61, 0.64, and 0.60 µg/kg/min, respectively.

No statistical difference was found between the epinephrine and norepinephrine-dobutamine for systemic hemodynamic measurements as seen in the following table from the published study report.

Table 6: Effects of epinephrine and norepinephrine-dobutamine on hemodynamic parameters

Group	Baseline	H1	H6	H12	H24
COPYRIGHT MATERIAL WITHHELD					

Values are given as mean ± SD
* $p < 0.01$ versus baseline
*No difference was observed between epinephrine and norepinephrine-dobutamine
MAP = mean arterial pressure; HR = heart rate; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure; CI = cardiac index; DO_2I = oxygen delivery index; VO_2I = oxygen consumption index

Six of 15 patients in the epinephrine group and 7 of 15 patients in norepinephrine-dobutamine group survived. The authors concluded that epinephrine is as effective as norepinephrine-dobutamine. Nevertheless, gastric mucosal acidosis and global metabolic changes observed in epinephrine-treated patients were consistent with a less adequate, although transient, splanchnic oxygen utilization.

Le Tulzo 1997: Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure: a preliminary descriptive study
Design: A prospective, descriptive study conducted to evaluate the potential advantage of epinephrine on right ventricular performance in 14 patients with septic shock unresponsive to fluid loading, dopamine, and dobutamine

Treatment: Epinephrine was started at an initial infusion rate of 0.1 µg/kg/min and was progressively increased in increments of 0.1 µg/kg/min to achieve a SAP ≥ 90 mmHg or a MAP ≥ 70 mmHg. The dose of epinephrine infused during the study ranged from 0.1 to 1 µg/kg/min. Hemodynamic measurements were obtained before and during epinephrine infusion, immediately following stabilization, and within 2 hours after epinephrine was started. Dopamine was started at an initial rate of 5 µg/kg/min and progressively increased. Dobutamine was used if the cardiac index was < 4 L/min/m^2 but was discontinued if SAP decreased by 20 mmHg. Once the criteria of septic shock resistant to the treatments were met, epinephrine was started.

Patients, 11 male and 3 female, had a mean age of 70 ± 14 years. Eleven patients were on mechanical ventilation. The duration of shock before the study was 18 ± 30 hours. In all patients, the epinephrine infusion significantly increased the MAP, cardiac index, stroke volume index, and right and left ventricular stroke work index without any change in systemic vascular resistance, heart rate, or pulmonary arterial occlusion pressure as shown in the following table from the published study report.

Table 7: Hemodynamic variables before (control) and during epinephrine infusion in 14 patients in refractory septic shock (mean ± SD)

Variables	Control	Epinephrine	Significance
COPYRIGHT MATERIAL WITHHELD			

RVEF = right ventricular ejection fraction; RVEDVI = right ventricular end-diastolic volume index; RVESVI = right ventricular end-systolic volume index; RVSWI = right ventricular stroke work index; RAP = right arterial pressure; MPAP = mean pulmonary arterial pressure; MAP = mean arterial pressure; PAOP = pulmonary artery occlusion pressure; SVR = systemic vascular resistance; SVI = stroke volume index; LVSWI = left ventricular stroke work index; CI = cardiac index; HR = heart rate; NS = not significant

The overall mortality related to septic shock was 64%. Right ventricular dysfunction is common in septic shock, as half (50%) of the patients in this study had severe depressed right ventricular function with marked right ventricular dilation and a decrease in right ventricular ejection fraction. The beneficial effect of epinephrine on the right ventricular function was observed solely in patients with previous right ventricular dysfunction as shown in Group A in the following table from the published study report. The major factor accounting for right ventricular performance improvement after the administration of epinephrine was an increase in myocardial contractility due to epinephrine's potent inotropic effect.

Table 8: The hemodynamic variables before (control) and during epinephrine infusion according to the presence (group A) or absence (group B) of right ventricular failure in refractory septic shock

Variables	Group A ($n = 7$)		Group B ($n = 7$)	
	Control	Epinephrine	Control	Epinephrine

COPYRIGHT MATERIAL WITHHELD

RVEDVI = right ventricular end-diastolic volume index; RVESVI = right ventricular end-systolic volume index; SVI = stroke volume index; RVEF = right ventricular ejection fraction; CI = cardiac index; RAP = right arterial pressure; MPAP = mean pulmonary arterial pressure; SPAP = systolic pulmonary artery pressure; RVSWI = right ventricular stroke work index; MAP = mean arterial pressure; PAOP = pulmonary artery occlusion pressure; LVSWI = left ventricular stroke work index; SVR = systemic vascular resistance; HR = heart rate

Right ventricular monitoring during severe septic shock permitted the identification of patients with right ventricular dysfunction who are difficult to identify with the usual measurements. Administration of epinephrine to these patients improves right ventricular performance with a rise in stroke volume index and right ventricular ejection fraction without an increase in right ventricular end-diastolic volume via a predominant effect on right ventricular contractility.

Duranteau 1999: Effects of epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock
Design: A randomized, controlled, crossover study conducted in 12 patients with septic shock to compare the effects of epinephrine, norepinephrine, and the combination of norepinephrine and dobutamine on systemic hemodynamic parameters and gastric mucosal perfusion using gastric tonometry and laser-Doppler flowmetry techniques.

The study consisted of 7 males and 5 females with a mean age of 54 ± 11 years who had clinical and laboratory parameters that fulfilled the criteria of septic shock. The study group consisted of patients who failed to respond to 20 µg/kg/min of dopamine. No significant differences were found for most parameters assessed as is shown in the following table from the published study report. However, the increase in gastric mucosal perfusion was higher with epinephrine and the combination of norepinephrine and dobutamine than with norepinephrine alone ($p < 0.05$).

Table 9: Evolution of the investigated parameters among the different treatments In the same patients

	NE	NE + Dobu	E
COPYRIGHT MATERIAL WITHHELD			

The authors concluded that both epinephrine and norepinephrine were effective in achieving hemodynamic stability in septic shock. A somewhat lower dose of epinephrine could achieve this same result, and without dobutamine.

Seguin 2002: Effects of epinephrine compared with the combination of dobutamine and norepinephrine on gastric perfusion in septic shock
Design: A randomized, parallel group study comparing epinephrine (N = 11) with the combination of dobutamine and norepinephrine (N = 11) on the gastric perfusion in patients with septic shock by examining the effects on systemic and pulmonary hemodynamics, hepatic function, and blood gases.

Treatment: Epinephrine or norepinephrine were titrated from 0.1 µg/kg/min and increased every 5 minutes by 0.2 µg/kg/min. Dobutamine was continuously infused at 5 µg/kg/min. The mean epinephrine dose was 0.3 ± 0.2 µg/kg/min. The effects of treatment were measured just before catecholamine infusion and when the MAP reached 70-80 mmHg. The mean age was 65 years in the epinephrine group and 70 years in the dobutamine-norepinephrine group. The results are shown in the following 2 tables from the published study.

Table 10: Systemic and pulmonary hemodynamics, gastric mucosal blood flow, and indocyanine green clearance between epinephrine and dobutamine-norepinephrine groups

	Epinephrine (n = 11)		*Dobutamine-norepinephrine (n = 11)*		*Statistical significance*		
						ANCOVA	
	Baseline	*Evaluation*	*Baseline*	*Evaluation*	*Student t test*	*Slopes*	*Treatment*

COPYRIGHT MATERIAL WITHHELD

Table 11: Arterial and mixed venous blood gas values and arterial lactate values between epinephrine and dobutamine-norepinephrine groups

	Epinephrine (n = 11)		*Dobutamine-norepinephrine (n = 11)*		*Statistical significance*		
						ANCOVA	
	Baseline	*Evaluation*	*Baseline*	*Evaluation*	*Student t test*	*Slopes*	*Treatment*
COPYRIGHT MATERIAL WITHHELD							

These results show no significant difference between the groups regardless of the systemic and pulmonary hemodynamic or blood gas variable considered. Nevertheless, compared with dobutamine-norepinephrine, epinephrine tended to induce greater values for cardiac index and oxygen transport. Epinephrine also induced significantly greater values of gastric mucosal blood flow but did not modify indocyanine green clearance. Also noteworthy was that the levels of arterial lactate were similar between the 2 treatment groups.

The authors concluded that in patients with septic shock, at doses that induced the same MAP, epinephrine at 5 µg/kg per minute enhanced more gastric mucosal blood flow than the combination of dobutamine and norepinephrine. This effect was probably the result of a higher cardiac index. The study also showed no differences in indocyanine green clearance between the groups. Therefore epinephrine and norepinephrine did not differ in their effects on hepatic function.

Levy 2005c: Cardiovascular response to dopamine and early prediction of outcome in septic shock: A prospective multiple-center study
Design: A prospective, observational study conducted in 110 adult patients with septic shock to compare the mortality rates between dopamine-sensitive and dopamine-resistant patients.

Treatment: Norepinephrine or epinephrine (0.5–5 µg/kg/min) with/without dobutamine (5-15 µg/kg/min) was administered to patients resistant to dopamine. Dopamine resistance was defined by a MAP < 70 mmHg despite the use of 20 µg/kg/min of

dopamine after volume resuscitation. If the patients were found dopamine-resistant, the intervention consisted of switching from dopamine to epinephrine or norepinephrine. Mean patients ages ranged from 58 to 63 years across the dopamine-sensitive and dopamine resistant groups. Reversal of shock was defined by a stable MAP > 70 mmHg for > 24 hours without catecholamine or additional volume loading. The type and dosage (µg/kg/min) of catecholamine after inclusion are reported for the dopamine-sensitive and dopamine-resistant groups in the following table from the published study report.

Table 12: Type and dosage (µg/kg/min) of catecholamine in dopamine-sensitive and dopamine resistant groups

Time After Inclusion	Dopa-S n = 44	Dopa-R n = 66
COPYRIGHT MATERIAL WITHHELD		

Of the 110 patients studied, 66 were observed to be resistant to dopamine (60%). Overall mortality rate was 59 of 110 (53.6%). The capacity of dopamine resistance to predict death was associated with a sensitivity of 84% and a specificity of 74%. At 24 hours, the association of dopamine resistance to a lactate level >3.5 mmol/L improved the prognostic value (sensitivity, 90%, specificity, 92%). Dopamine sensitivity is associated with decreased mortality rate.

Seguin 2006: Dopexamine and norepinephrine versus epinephrine on gastric perfusion in patients with septic shock: a randomized study
Design: A randomized, open-label, parallel-group study to compare the effects of dopexamine norepinephrine (N = 12, 9 male, 3 female) with those of epinephrine (N = 10, 8 male, 2 female) on gastric mucosal blood flow in patients with septic shock.

Treatment: Epinephrine and norepinephrine were titrated from 0.2 µg/kg/min with 0.2 µg/kg/min increments every 3 minutes until the MAP reached 70 to 80 mmHg; dopexamine (a structural and synthetic analog of dopamine) was titrated from 0.5 µg/kg/min with 0.5 µg/kg/min increments every 3 minutes. Doses could be decreased for a MAP > 80 mmHg. Median epinephrine doses at the times of investigation ranged from 0.17 to 0.19 µg/kg/min.

This study was conducted to compare the effects of dopexamine-norepinephrine with those of epinephrine on gastric mucosal blood flow because the microcirculatory blood flow and gut perfusion are important in the development of multiple organ failure in septic shock. The gastric mucosal blood flow was measured by laser-Doppler. The mean age was 67 years in the epinephrine group and 65 years in the norepinephrine plus dopexamine group.

The mortality rate at day 28 was 3/10 (30%) in the epinephrine group and 2/12 (17%) in the norepinephrine plus dopexamine group. At day 90, the mortality rate was 4/10 (40%) in the epinephrine group and 3/12 (25%) in the norepinephrine plus dopexamine group. With regard to systemic hemodynamics, epinephrine induced greater heart rate, cardiac output, oxygen delivery, and oxygen consumption than the combination of dopexamine and norepinephrine. These effects express the well-known strong β1-adrenergic stimulation induced by epinephrine. Compared to epinephrine, dopexamine plus norepinephrine showed greater enhancement of gastric mucosal blood flow. No difference was observed on oxidative stress. These results are shown in the following table from the published study.

Table 13: Effects of epinephrine and dopexamine-norepinephrine on hemodynamic and oxygenation parameters and gastric mucosal blood flow

Parameter	Group	T_0	T_1	T_2	T_3	*p* (time effect)	*p* (treatment effect)	*p* (interactic

COPYRIGHT MATERIAL WITHHELD

Annane 2007: Norepinephrine plus dobutamine vs. epinephrine alone for management of septic shock: a randomized trial

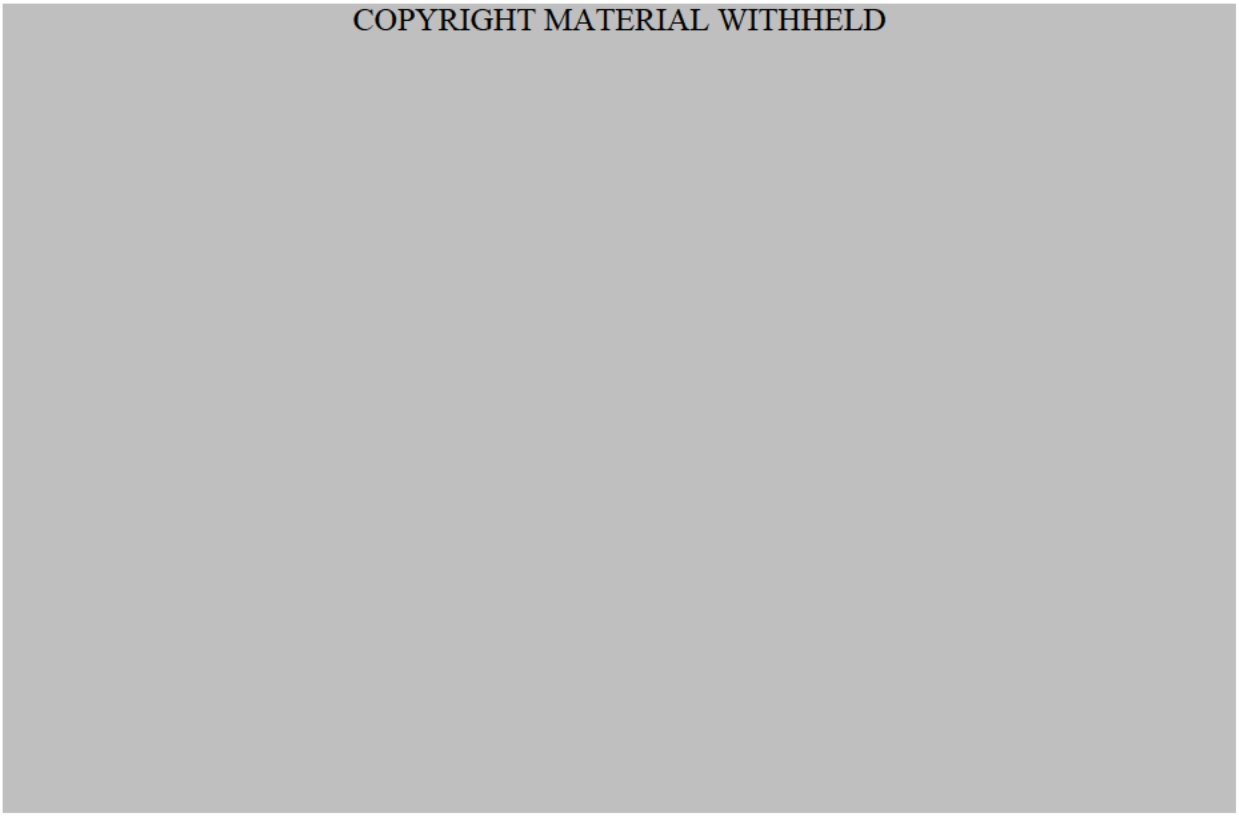
Up to the date of this trial, the recommended treatment for hypotension in septic shock was to use first dopamine or norepinephrine. This prospective, multicenter study was conducted to compare the efficacy and safety of norepinephrine plus dobutamine with epinephrine alone in septic shock.

Design: A multicenter, randomized, double-blind clinical trial conducted in 330 adult patients with septic shock to compare the efficacy and safety of norepinephrine plus dobutamine (N = 169) with those of epinephrine alone (N = 161).

Treatment: Epinephrine (approximate mean dose 1 µg/kg/min for days 1 and 2 and 0.5 µg/kg/min for days 3 to 10) or norepinephrine plus dobutamine titrated to achieve a MAP of at least 70 mmHg. The starting epinephrine dose was 0.2 µg/kg/min.

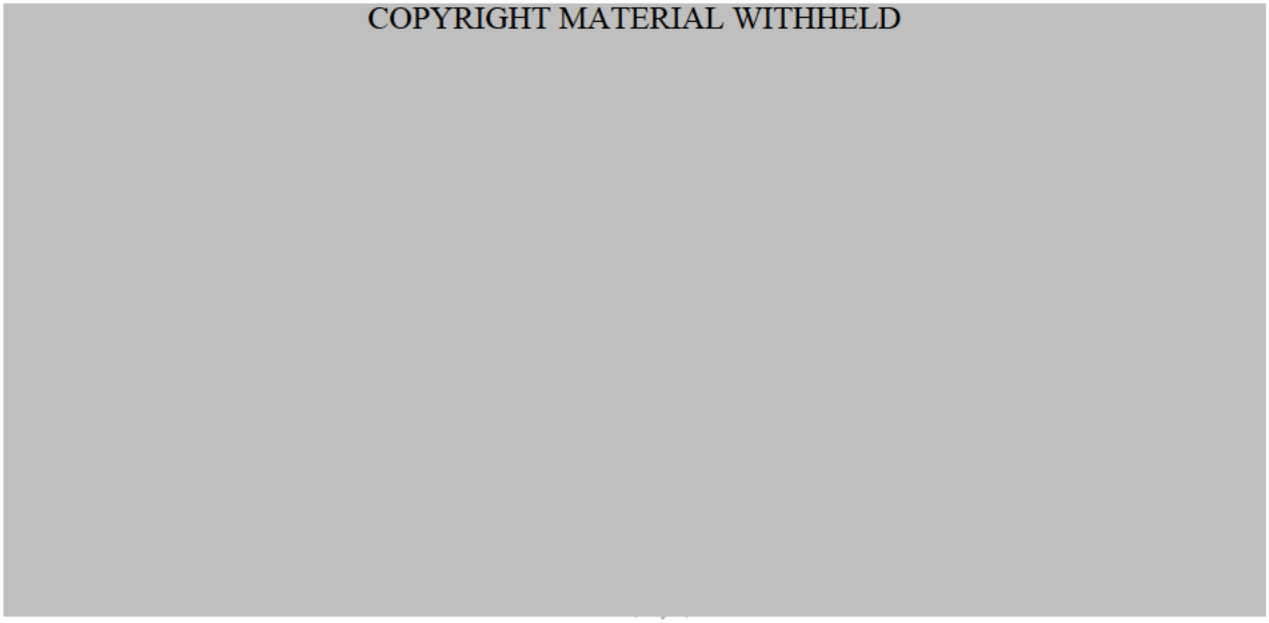
The primary outcome was the 28-day all-cause mortality. The multiple secondary endpoints included survival distribution from randomization to day 90; mortality rates at day 7, day 14, at discharge from intensive care and hospital, and at day 90; systemic hemodynamics; arterial pH and lactate; Sequential Organ Failure Assessment (SOFA) score; time to hemodynamic success defined as MAP above 70 mmHg for at least 12 hours; and time to vasopressor withdrawal (first interruption of the vasopressor for at least 24 hours). The doses of vasopressors needed were not different between the 2 treatment groups as shown in the following figure from the published study.

Figure 2: Drug doses over time of epinephrine or norepinephrine



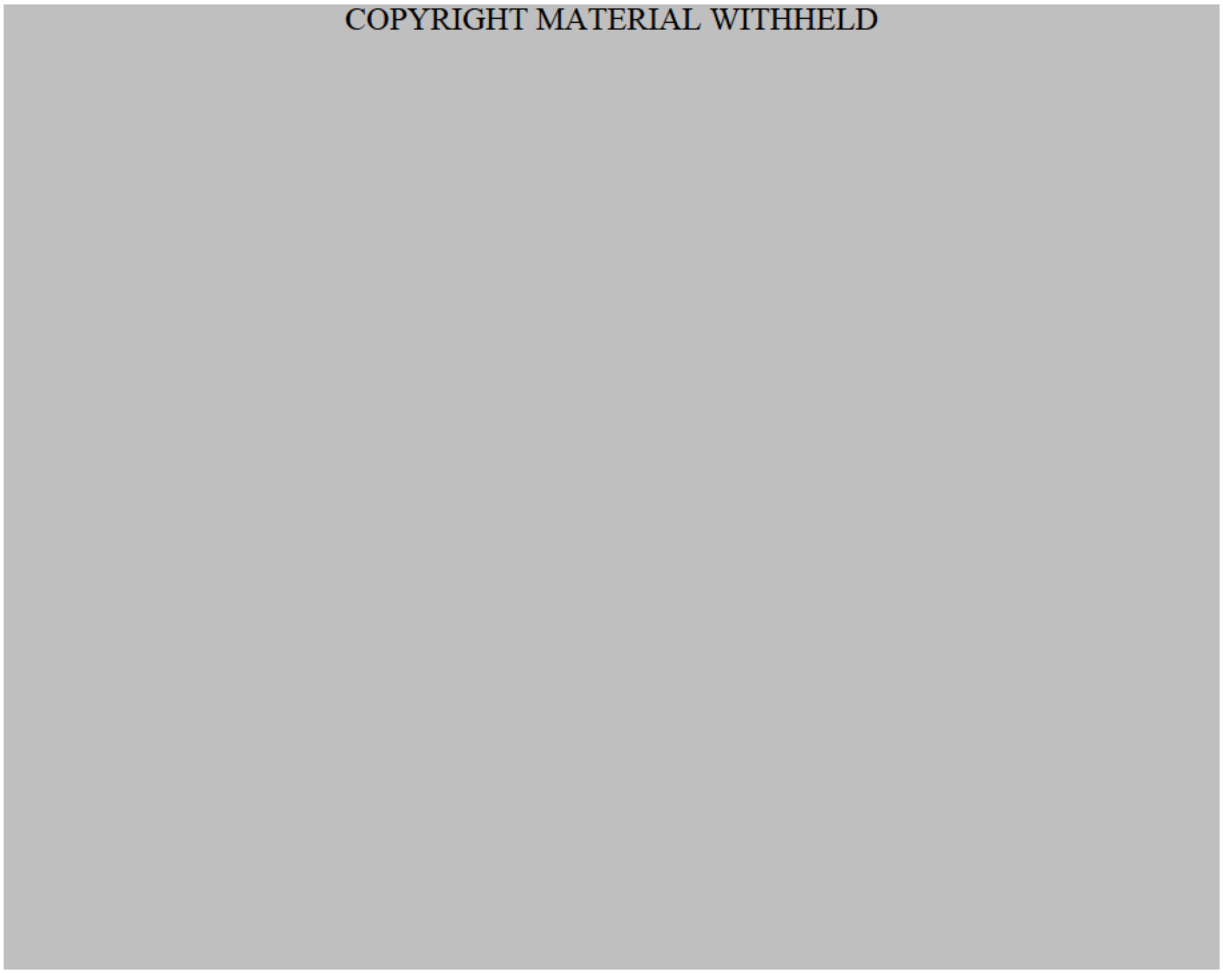
Following randomization, the MAP increased to the same extent in both groups as shown in the following figure from the published study.

Figure 3: Effects of treatment on mean arterial pressure



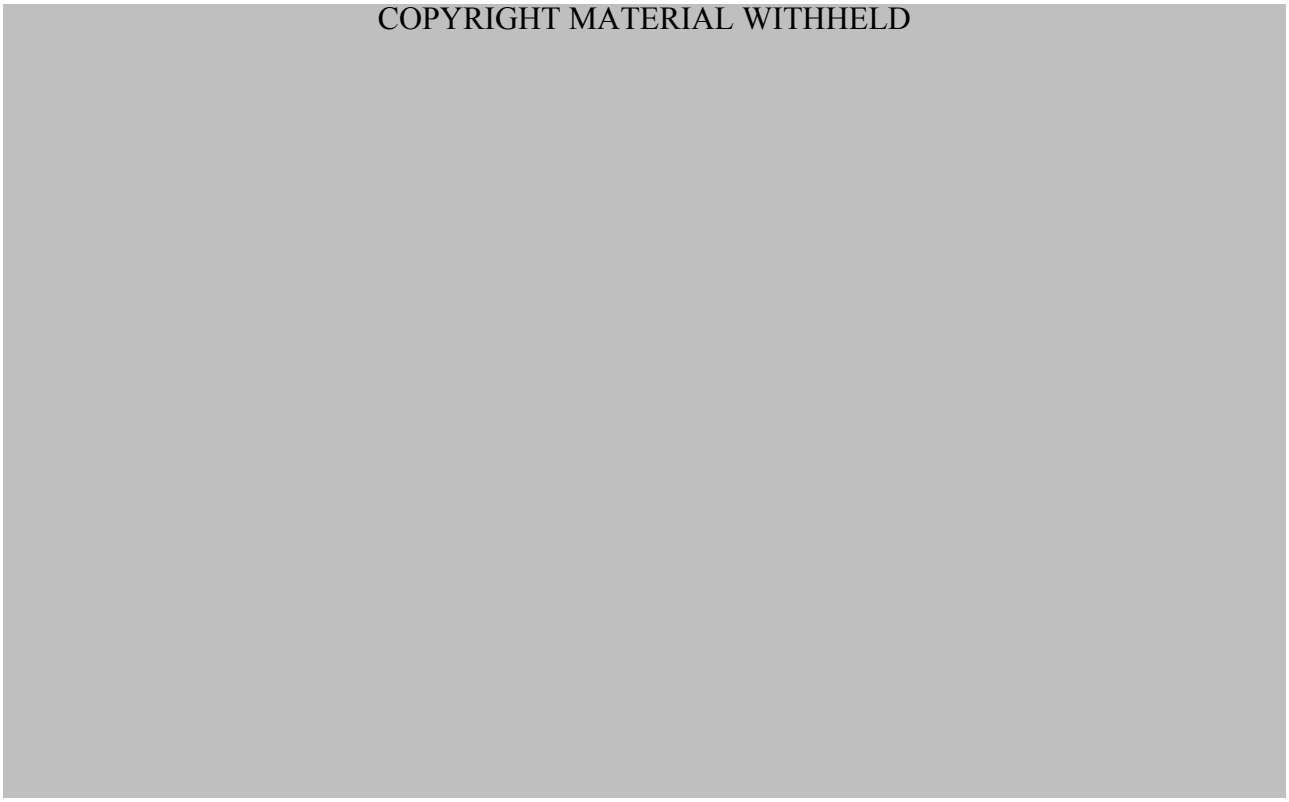
The results for time to hemodynamic success and vasopressor withdrawal are presented in the following figure from the published study and show no significant differences between the 2 groups for these measures.

Figure 4: Kaplan-Meier plots of time to (A) hemodynamic success and (B) vasopressor withdrawal



There was no significant difference between the two groups in mortality rates. Comparing epinephrine to norepinephrine plus dobutamine, there were 64 (40%) versus 58 (34%) deaths at day 28 (p = 0.31), 75 (47%) versus 75 (44%) deaths at discharge from intensive care (p = 0.69), 84 (52%) versus 82 (49%) deaths at hospital discharge (p = 0.51), and 84 (52%) versus 85 (50%) deaths by day 90 (p = 0.73). Survival from randomization to day 90 is presented in the following figure from the published study.

Figure 5: Survival from Day 90



The epinephrine group had a lower arterial pH in the first 4 days and higher arterial lactate concentrations on the first day. However, these metabolic effects recovered within 4 days and there was no difference between treatments for time to hemodynamic stabilization, recovery of organ dysfunction, or on survival. The authors concluded that there was no evidence for a difference in short-term or long-term efficacy and safety between epinephrine alone and norepinephrine plus dobutamine for the management of septic shock.

Myburgh 2008: Australian CAT study: a comparison of epinephrine and norepinephrine in critically ill patients

Design: A multicenter, double-blind, randomized, controlled trial conducted to determine whether there was a difference between epinephrine (N = 139 [76 had septic shock]) and norepinephrine (Levophed; N = 138 [82 had septic shock]) in achieving the MAP goal in a heterogeneous population of ICU patients requiring vasopressors for any cause at randomization. Patients with septic shock (N = 158; septic patients who required study drug were considered to have septic shock) and acute circulatory failure (N = 128) were analyzed separately.

Treatment: Maximum doses to achieve the MAP were similar for both drugs and were about 13 µg/min (0.19 µg/kg/min in a 70 kg patient) for the first 16 hours and down to about 5 µg/min (0.07 µg/kg/min in a 70 kg patient) after day 2.

The study included 167 males and 110 females approximately 60 years old. Of patients with septic shock, 76 received epinephrine and 82 received norepinephrine. The primary outcome was the achievement of the MAP goal for more than 24 hours without vasopressors. Secondary outcomes were 28 and 90-day mortality.

In the subgroup of patients with severe sepsis at baseline (158/277), there was no difference in the median time to achieve the MAP goal between epinephrine (35.1 hours; IQR 16.7–75 hours; n = 76) and norepinephrine (50.0 h; IQR 18.2–127.5 hours; n = 82) (hazard ratio 0.81; 95% CI 0.59–1.12; p = 0.18). For these patients, there was no difference in the number of vasopressor-free days between epinephrine (26.3 days; IQR 17.2–27.3) and norepinephrine (24.2 days; IQR 7.7–26.5) (p = 0.13). There was no significant difference in 28 or 90-day mortality between the 2 drugs in the overall group or in the severe sepsis or acute circulatory failure groups as shown in the following table from the published study.

Table 14: Outcomes between all patients, patients with severe sepsis and patients with acute circulatory failure treated with epinephrine or norepinephrine

Variables	Epinephrine	Norepinephrine	Hazard ratio	95% CI	*P*
COPYRIGHT MATERIAL WITHHELD					

The study found no statistically significant differences in the time to achievement of a target MAP and other hemodynamic resuscitation endpoints between epinephrine and norepinephrine. In the subgroups of patients with severe sepsis and acute circulatory failure, there was no difference in the time to the achievement of target MAP or in the number of vasopressor-free days between the 2 drugs. Epinephrine was associated with the development of significant but transient metabolic effects that prompted the withdrawal of 18/139 (12.9%) patients from the study. The authors concluded that overall there was no difference in the hemodynamic responses to epinephrine and norepinephrine and suggest that either of these drugs may be used effectively in the ICU.

Wutrich 2010: Early increase in arterial lactate concentration under epinephrine infusion is associated with a better prognosis during shock
Design: A retrospective study of 100 consecutive ICU patients in the shock state irrespective of etiology (82% had septic shock) was conducted to determine whether epinephrine-induced early (within 4 hours) an increase in arterial lactate concentration which can prognosticate a good outcome during shock state.

Treatment: 100% of the included patients received epinephrine, 19% received norepinephrine, and 20% received dobutamine. Dosing data are presented through hour 4; study measurements are presented for 48 hours of treatment. For survivors, the mean dose was 0.258 ± 0.03 µg/kg/min at hour 0 and 0.469 ± 0.06 µg/kg/min at hour 4, and for nonsurvivors, the mean dose was 0.394 ± 0.06 µg/kg/min at hour 0 and 1.15 ± 0.11 µg/kg/min at hour 4.

At admission, the arterial lactate concentration was elevated and was further increased upon epinephrine administration, reaching a peak at hour 4 (8.22 ± 3.66). Survivors (N = 28) had an arterial lactate concentration of 3.27 ± 0.58 at H0 and 7.35 ± 0.75 at H4 after epinephrine infusion, compared to nonsurvivors (N = 72) with an arterial lactate concentration of 5.72 ± 0.61 at H0 and 8.64 ± 0.60 at H4 after infusion. The mean Δ lactate was 137 (85-287) for survivors compared to a mean Δ lactate of 45 (12-115) in nonsurvivors ($p < 0.0001$). When patients were stratified according to their outcome, nonsurvivors displayed the same pattern as survivors, although with a significant upward shift in values as shown in the following table from the published study report.

Table 15: Multivariate logistic regression modeling

Variable	Coefficient	SE	OR (95% CI)	*P*
COPYRIGHT MATERIAL WITHHELD				

At a value of 100%, Δ lactate predicted death, with a 71% sensitivity (95% CI, 51%-87%) and a 67% specificity (95% CI, 43%-85%). The Kaplan-Meier survival analysis confirmed this finding, with a 52.4% death rate among patients with Δ lactate greater than 100, compared to an 84.7% death rate when Δ lactate was less than 100 (log-rank

test, p = 0.0002). The key result of the study was the ability to increase aerobic glycolysis and, therefore, to produce lactate upon epinephrine stimulation during shock state is associated with a better prognosis, evoking a preserved physiological response to catecholaminergic stress. This study also found that after 4 hours of epinephrine administration, the higher the exogenous epinephrine-associated increase in lactate, the better the prognosis.

Lactate changes from epinephrine use are also discussed later in the Safety Section.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In these studies cited from the literature the doses given to patients with septic shock were titrated to effect most often using the MAP. The dose varied within and between studies, but the reported doses generally ranged between 0.05 to 2.0 µg/kg/min which is the range proposed by the sponsor. Treatment usually started at low doses and generally did not exceed 2.0 µg/kg/min. The dosing duration could last for hours or days and generally continued until achievement of the MAP levels was maintained for a pre-specified period of time.

7 Review of Safety

Safety Summary

Epinephrine in the treatment of septic shock is only part of the septic shock treatment as patients also need fluid replacement and antibiotics. Epinephrine in this setting will be utilized in an intensive medical care unit with monitors for heart rate, EKGs, and heart pressures. All drugs utilized for increasing the blood pressure in this situation have side effects. However, the benefits of the use of epinephrine generally outweigh its risks as shown in this literature review.

7.1 Methods

The sponsor primarily relies on the Twinject label for safety. However, epinephrine is used in Twinject for the treatment of severe allergic reactions usually with one or two injections and for short term treatment. In this submission epinephrine is given for the treatment of hypotension associated with septic shock and is given intravenously for hours to many days.

Additionally, the sponsor has submitted articles from the literature. In the above studies that were cited for efficacy, only a few of these studies provided information regarding safety. Some of the studies cited by the sponsor include patients who did not have

septic shock but were treated for shock of another etiology. For the study design of the literature references in the safety section, please refer to the efficacy section above for that study. The studies again will be presented in historical order as the treatment of septic shock is evolving. To supplement the Twinject label and the literature provided by the sponsor, this reviewer looked at the 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. No articles on safety were found regarding the use of epinephrine for long periods of time.

Bollaert 1990
Design: A prospective study performed to assess the effects of epinephrine on hemodynamic and metabolic variables in 13 septic shock patients who remained hypotensive after both fluid loading and dopamine administration. Study measurements were taken for only 1 hour.

Treatment: A continuous infusion of epinephrine was started at a rate of 0.5 µg/kg/min; after 30 minutes, if systolic pressure was still below 90 mmHg, this was increased to 1 µg/kg/min. The report stated that no arrhythmias occurred except a brief ventricular tachycardia in one patient.

Lipman 1991
No specific data for adverse events were reported in this study. However, the authors state that no arrhythmias apart from tachycardia that was already present were documented and that they could not document any myocardial damage from the high epinephrine doses or the long duration of epinephrine administration.

Wilson 1992
In this prospective study in 15 adult patients, epinephrine was infused starting at 0.025 µg/kg/min and increased by 0.025 µg/kg/min every 20 minutes. The maximum epinephrine infusion rate ranged from 0.05 to 0.3 µg/kg/min. No arrhythmias or any significant electrocardiogram (ECG) changes indicating myocardial ischemia were noted.

Moran 1993
This was a prospective clinical study in which 9 male and 9 female adult patients with septic shock received epinephrine with a maximum dose range of 3 to 27 µg/min (0.042 to 0.39 µg/kg/min in a 70 kg patient). The authors stated that epinephrine infusions were well tolerated with no clinically important ventricular or supraventricular dysrhythmias during the study.

Illi 1995: The effect of entacapone on the disposition and hemodynamic effects of intravenous isoproterenol and epinephrine.
Design: A randomized, 2-group, parallel, double-blind pharmacodynamics study conducted in 11 healthy male volunteers to investigate whether entacapone, a catechol-O-methyltransferase (COMT) inhibitor, can potentiate the hemodynamic responses and increase the plasma concentrations of intravenously infused isoproterenol, a β agonist, and epinephrine in healthy individuals.

Treatment: Subjects were given either a single dose of 400 mg entacapone or placebo 30 minutes before the start of isoproterenol or epinephrine infusions. Four dosages of epinephrine (1.5, 3, 6, or 12 µg/min) and isoproterenol (0.5, 1, 1.5, or 2 µg/min) were infused (5 minutes for each level). Palpitations were the most frequently reported adverse events. During the epinephrine infusion, 2 of 6 subjects (33%) reported palpitations after placebo and 4 of 8 subjects (50%) reported palpitations after entacapone administration. During the isoproterenol infusion, 2 of 6 subjects (33%) complained of palpitations after placebo, and 6 of 8 subjects (75%) complained of palpitations after entacapone administration. Because of these instances of tachycardia, the study was terminated early without the planned crossover.

Day 1996 (patients with severe sepsis or malaria) 10/23 had severe sepsis and 9 of these had shock on admission.
Design: An open-label, randomized, crossover study performed in Vietnam to compare the effects of stepped doses of epinephrine and dopamine on the hemodynamic and acid-base status of 23 critically ill patients, 10 with severe sepsis and 13 with severe malaria.

Treatment**:** Following fluid volume loading, patients were monitored for 45 minutes. Patients who were still in shock after fluid loading received epinephrine or dopamine titrated rapidly over 10 to 15 minutes to a dose that maintained systolic blood pressure above 80 mmHg. The administration of epinephrine was discontinued in 16 patients due to development of lactic acidosis.

Levy 1997
Design: A prospective, randomized clinical trial to compare the effects of norepinephrine and dobutamine (N = 15) to epinephrine (N = 15) on hemodynamics, lactate metabolism, and gastric tonometric variables in hyperdynamic dopamine-resistant septic shock.

Treatment: Epinephrine and norepinephrine infusions were started at 0.3 µg/kg/min and increased on the MAP at 5-minute intervals to obtain a MAP above 80 mmHg after the first hour as dopamine was stopped. The authors reported that no arrhythmias occurred.

De Backer 2003
Design A prospective, randomized, open-label study performed in 20 patients with septic shock to assess the effects of different doses of dopamine, norepinephrine, and epinephrine on the splanchnic circulation.

Treatment: Patients with hypotension resistance to intravenous fluids were treated first with dopamine then were randomly assigned to receive norepinephrine or epinephrine to replace dopamine. The patients receiving norepinephrine were then switched to epinephrine and patients receiving epinephrine were switched to norepinephrine. Epinephrine and norepinephrine doses were adjusted to maintain constant MAP above 65 mmHg.

The mean age was about 68 years with 15 males and 5 females. The systemic circulation (pulmonary artery catheter), splanchnic circulation (indocyanine green dilution and hepatic vein catheter) and gastric mucosal partial pressure of carbon dioxide (gas tonometry) were measured during each of the catecholamines. The hemodynamic data are presented in the following table from the published study. The MAP was similar with the 3 agents for moderate and severe shock. In moderate shock, the cardiac index was similar for dopamine and norepinephrine but greater with epinephrine ($p < 0.01$ vs. dopamine and norepinephrine). Splanchnic blood flow was similar with the 3 agents. The gradient between mixed-venous and hepatic venous oxygen saturations was lower with dopamine than with norepinephrine and epinephrine. The partial pressure of carbon dioxide gap was similar with the 3 agents.

In severe shock, cardiac index was higher ($p < 0.01$), but splanchnic blood flow was lower ($p < 0.05$), with epinephrine than with norepinephrine. Epinephrine increased the mixed- venous and hepatic venous oxygen saturation gradient but did not alter the partial pressure of the carbon dioxide gap.

Table 16: 6 Principal hemodynamic data between the 3 agents

	Dopamine	Norepinephrine	Epinephrine	Group × Drug[a]
COPYRIGHT MATERIAL WITHHELD				

The authors concluded that dopamine and norepinephrine have similar hemodynamic effects, but epinephrine can impair splanchnic circulation in severe septic shock, but not in moderate shock. Norepinephrine and epinephrine may have similar effects on gastric mucosal partial pressure of carbon dioxide.

Levy 2005a
Design: A prospective study conducted in 14 patients with septic shock using in-vivo microdialysis to test whether inhibition of Na+/K+ ATPase with ouabain infusion can reduce muscle lactate production under aerobic conditions.

Treatment: Epinephrine (N = 8) and norepinephrine (N = 6). Epinephrine doses were decreased from 0.9 µg/kg/min (SD 0.1) at 0 hours to 0.4 µg/kg/min (SD 0.1) at 24 hours. Norepinephrine doses were decreased from 1.0 µg/kg/min (SD 0.1) at 0 hours to 0.5 µg/kg/min (SD 0.1) at 24 hours. Data for epinephrine and norepinephrine were pooled.

Patients (mean age of 65 years) had 2 microdialysis probes inserted into the quadriceps muscles and infused with lactate-free Ringer's solution in the absence or presence of 10-7 mol/L ouabain, a specific inhibitor of Na+/K+ ATPase. Lactate and pyruvate concentrations were measured in both the dialysate fluid and arterial blood samples. All the patients were mechanically ventilated and 10 had bicarbonate hemofiltration. The pressure of carbon dioxide (gas tonometry) was measured during dopamine (moderate shock only) and during norepinephrine and epinephrine administration (moderate and severe shock groups).

Blood lactate fell within the 24-hour study period. Muscle lactate concentrations were always higher than arterial lactate concentrations during the study. Infusion with ouabain totally abolished the gradient between muscle and arterial lactate concentrations ($p = 0.0001$). Evidence seems to implicate an accelerated aerobic glycolysis, a definite state when the rate of glucose metabolism exceeds the oxidative capacity of the mitochondria. The rise in pyruvate concentration will ultimately drive lactate production by a mass effect. These findings lend support to the notion of muscle lactate production during septic shock. Lactate, instead of being regarded only as a marker of hypoxia, might be an important metabolic signal**.**

Annane 2007
Design: A multicenter, randomized, double-blind clinical trial conducted in 330 adult patients with septic shock to compare the efficacy and safety of norepinephrine plus dobutamine (N = 169) with epinephrine alone (N = 161).

Treatment: Epinephrine (approximate mean dose 1 µg/kg/min for days 1 and 2 and then 0.5 µg/kg/min for days 3 to 10) or norepinephrine plus dobutamine was titrated to achieve a MAP of at least 70 mmHg. The starting epinephrine dose was 0.2 µg/kg/min.

There were no significant differences between the groups in the rates of severe arrhythmias, cerebrovascular or myocardial events, limb ischemia, or any other side effects related to catecholamine administration as shown in the following table from the published study. There was no evidence for a difference in short-term or long-term safety between epinephrine alone and norepinephrine plus dobutamine in the management of septic shock.

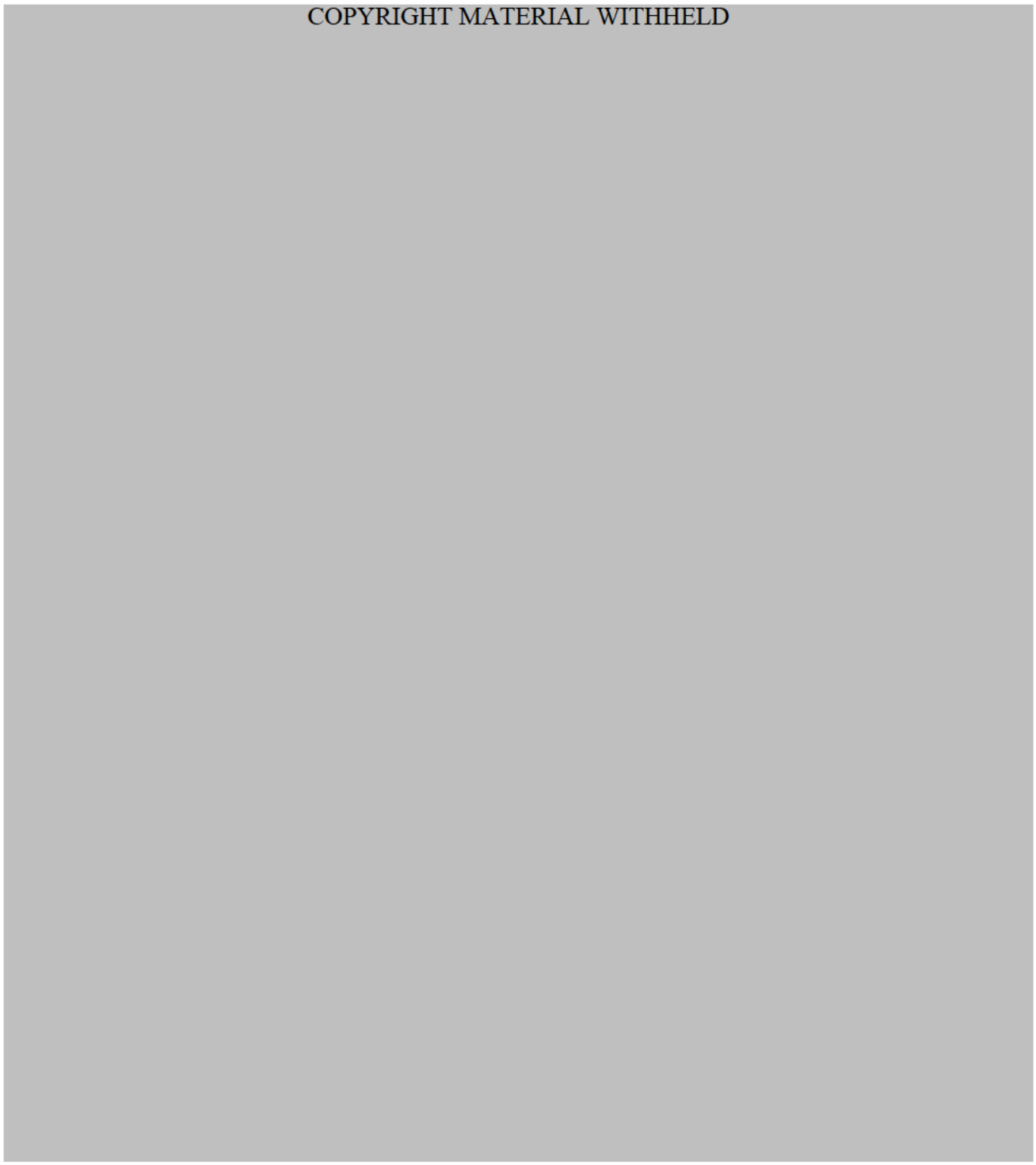
Table 17: Serious adverse events

	Overall (n=330)	Epinephrine (n=161)	Norepinephrine plus dobutamine (n=169)
COPYRIGHT MATERIAL WITHHELD			

Myburgh 2008 (patients needing vasopressors for any cause; 76/139 with septic shock)
Design: A multicenter, double-blind, randomized, controlled trial conducted to determine whether there was a difference between epinephrine (N = 139 [76 had septic shock]) and norepinephrine (Levophed; N = 138 [82 had septic shock]) in achieving a MAP goal in a heterogeneous population of intensive care (ICU) patients requiring vasopressors for any cause at randomization. Patients with septic shock (N = 158; septic patients who required study drug were considered to have septic shock) and acute circulatory failure (N = 128) were analyzed separately.

Treatment: A MAP goal of at least 70 mmHg was used. The study drug was used for the duration of the ICU admission until the MAP goal was achieved for greater than 24 hours without study drug, death, or discharge. Epinephrine was associated with the development of significant tachycardia and lactic acidosis that developed within the initial 4 hours after randomization and was sustained for the first 24 hours of the study treatment. Additionally there were increased insulin requirements, following which there was no difference between the 2 drugs which is shown in the following figure from the published study.

Figure 6: Comparisons between the epinephrine and norepinephrine on heart rate (top panel); and arterial lactate (middle panel) from baseline during the initial 16 hours (1–16 h) of infusion and the maximum daily level during the initial 4 days (D1–D4) of infusion period



A total of 22 patients were withdrawn from study treatment by the treating clinician: 18/139 (12.9%) in the epinephrine group and 4/138 (2.8%) in the norepinephrine group (p = 0.002). Lactic acidosis (7/18 for epinephrine vs. 2/4 for norepinephrine), tachycardia (4/18 vs. 1/4), and inability to achieve the prescribed parameters (5/18 vs. 1/4) were cited as the most common reason for withdrawal from the study treatment. There was no difference in the incidence of other severe adverse events, specifically supra- or ventricular tachyarrhythmias between the 2 groups.

The use of epinephrine was associated with significant but transient metabolic effects and tachycardia that prompted clinicians to withdraw a number of patients receiving epinephrine from the study. This study demonstrated that epinephrine-induced lactic acidosis was not associated with loss of hemodynamic efficacy or the development of new organ dysfunction.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There were no published studies included in this literature submission specifically dealing with the safety of the use of epinephrine in the treatment of hypotension associated with septic shock. The articles reviewed above for efficacy provided very little safety information.

7.2 Adequacy of Safety Assessments

No articles were found which specifically reviewed the effects of the long term use for hours or days of epinephrine use for the treatment of hypotension in septic shock.

7.3 Major Safety Results

7.3.1 Deaths

It is difficult to calculate deaths from epinephrine use as the illness that is being treated, septic shock, has such a high mortality rate. The relative mortality rate of epinephrine and other septic shock treatments such as norepinephrine can be seen in the results of the active-controlled studies. In a multicenter, randomized, double-blind study conducted in 330 adult patients with septic shock, mortality rates for epinephrine were similar to those with norepinephrine plus dobutamine (**Annane 2007**). At day 28, 40% of epinephrine versus 34% of norepinephrine patients had died, and by day 90, 52% of epinephrine versus 50% of norepinephrine patients had died.

There were three studies which reported the frequency of deaths:

- **Day 1996:** In an open-label, randomized, crossover study conducted in 23 patients with severe sepsis or malaria who received epinephrine and dopamine, 3/10 patients with severe sepsis and 3/13 patients with severe malaria died.

- **De Backer 2003:** In a randomized, open-label study conducted in 20 patients with septic shock, 8/10 patients with severe shock and 6/10 patients with moderate shock died. Those with septic shock resistant to dopamine were considered to have severe shock. Separate mortality results for epinephrine and norepinephrine were not reported

- **Levy 2005a:** In a study including 14 patients with septic shock who were treated with epinephrine or norepinephrine (mortality results were reported for both groups combined), 10 of 14 patients survived the septic episode.

7.3.2 Nonfatal Serious Adverse Events

The **Annane (2007)** study which is cited above several times reported serious adverse events. Rates of adverse events with epinephrine were compared to those with norepinephrine plus dobutamine. The most common (> 5%) serious adverse events reported during catecholamine infusion were supraventricular tachycardia > 150 bpm (12% of 161 patients for epinephrine and 13% of 169 patients for norepinephrine plus dobutamine) and ventricular arrhythmias (7% for epinephrine and 5% for norepinephrine plus dobutamine). Following catecholamine infusion, arrhythmias occurred in 4% of patients in each group. Other serious adverse events reported included acute coronary event, limb ischaemia, stroke, central nervous system bleeding, other neurological sequelae, and “others” as shown in the Table 17 above. There were no significant differences between the 2 groups in rates of serious adverse events related to catecholamine administration.

This reviewer found a number of case reports in the literature regarding large accidental doses of intravenous epinephrine with serious and potentially fatal consequences. These reports include myocardial ischemia and infarction, cardiomyopathy, pulmonary edema, and renal insufficiency. **(Novey, Ersoz, Karch, Fyfe, Ferry)**

7.3.3 Dropouts and/or Discontinuations

This would be difficult to access as each study was evaluated for a different period of time and there were many deaths secondary to the underlining illness, septic shock.

7.3.4 Significant Adverse Events

There are important side effects reported in the literature which include the following:

- Cardiac arrhythmia especially those patients suffering from heart disease, organic heart disease, or who are receiving drugs that sensitize the myocardium (**Mackie 1991; Brock 2003**).

- Hyperlactemia: administration of epinephrine may produce transient hyperlactemia and metabolic acidosis.

- Pulmonary edema: there is a risk of pulmonary edema because of the peripheral constriction and cardiac stimulation produced by epinephrine, (**Chen 1974**).

7.3.5 Submission Specific Primary Safety Concerns

The patients in these studies were treated in Intensive Care Units and were therefore carefully monitored for their blood pressure, EKG, heart pressures, and the metabolic effects of the drugs.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The common adverse effects are the same as the serious adverse effects discussed above.

7.4.2 Laboratory Findings

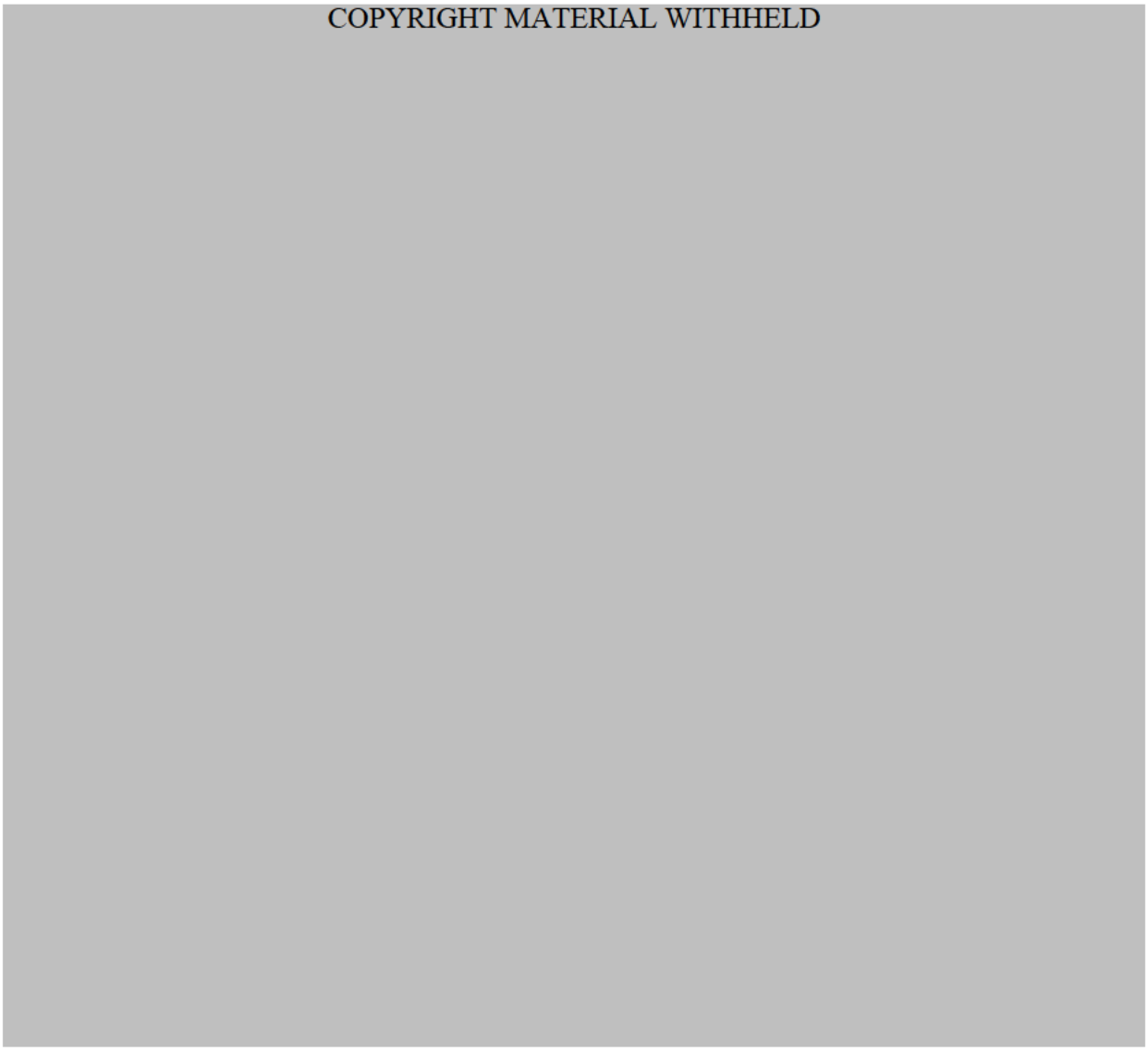
A concern with the use of epinephrine in septic shock is the development of an increase in lactic acid. The use of epinephrine in septic shock as a first line agent has been questioned because of its association with increased lactate levels. Originally this was viewed as evidence of tissue hypoxia, inadequate oxygen delivery associated with hypoperfusion.

There was a prospective study by **Levy (2005a)** conducted in 14 patients with septic shock using in-vivo microdialysis to test whether inhibition of Na+/K+ ATPase with ouabain infusion can reduce muscle lactate production under aerobic conditions. Epinephrine doses (N=8) decreased from 0.9 µg/kg/min (SD 0.1) at 0 hours to 0.4 µg/kg/min (SD 0.1) at 24 hours; norepinephrine (N=6) doses decreased from 1.0 µg/kg/min (SD 0.1) at 0 hours to 0.5 µg/kg/min (SD 0.1) at 24 hours. The data were pooled.

The patients (mean age of 65 years) had 2 microdialysis probes inserted into their quadriceps muscles and lactate and pyruvate concentrations were measured in both the dialysate fluid and arterial blood samples. All patients were mechanically ventilated. Blood lactate fell within the 24-hour study period. Muscle lactate concentrations were always higher than arterial lactate concentrations during the study. Infusion with ouabain totally abolished the gradient between muscle and arterial lactate concentrations ($p = 0.0001$). Lactate to pyruvate ratios were similar in both blood and muscle ($p = 0.28$) and remained unchanged during ouabain infusion. The authors state that evidence seems to implicate accelerated aerobic glycolysis induced by an endogenous or exogenous catecholamine. They propose that the high rate of aerobic glycolysis under epinephrine stimulation could provide some help to organs, such as the heart, wounded tissue, or brain. Lactate therefore instead of being regarded only as a marker of hypoxia, might be an important metabolic signal.

In the study by **Annane (2007)** the epinephrine group had lower arterial pH in the first 4 days and higher arterial lactate concentrations on the first day. However, these metabolic effects recovered within 4 days and had no effect on the time to hemodynamic stabilization, recovery of organ dysfunction, or on survival as shown in the following figures from the published study.

Figure 7: Effects of treatment on arterial ph and arterial lactate concentration



It has been shown that the accumulation of lactate during sepsis is due to the increased rate of pyruvate production. Epinephrine infusion is associated with an increase in lactate concentration not only in septic conditions but also under fully aerobic, such as in healthy volunteers at rest and during exercise. The temporary increase in blood lactate associated with exogenous epinephrine infusion is believed associated with increased aerobic glycolysis and not hypoxia. Epinephrine induced lactate production is a transient phenomenon peaking at about 4 to 6 hours and persisting 12 to 18 hours (**Wutrich 2010**).

An additional laboratory finding with giving epinephrine intravenously is an increase in the blood sugar as reported by **Beck (1985).** Patients with insulin dependent diabetes showed threefold increase in their glucose due to their inability of to augment insulin secretion. Also, hypokalemia has been documented in cases of accidental overdose.

7.4.3 Vital Signs

Epinephrine is a potent vasopressor drug. If a pharmacological dose is given by an intravenous route, it evokes a rapid rise in the blood pressure that is proportional to the dose. The increase in systolic pressure is greater than the increase in diastolic pressure, which causes the pulse pressure to increase.

The pulse rate which at first accelerates may be slowed at the height of the rise of blood pressure by compensatory vagal discharge.

7.4.4 Electrocardiograms (ECGs)

Epinephrine has been reported to cause ECG changes including a decrease in T-wave amplitude in all leads in normal persons (**Tanaka 2001**).

7.5 Other Safety Explorations

7.5.3 Drug-Demographic Interactions

According to the approved labeling for the listed drug Twinject and additional sources in the literature, elderly patients are at increased risk of adverse reactions, including those caused by overdosage.

7.5.4 Drug-Disease Interactions

From the Twinject label:
“Epinephrine should be administered with caution to patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In patients with coronary insufficiency or ischemic heart disease, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. It should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.”

Epinephrine should be used cautiously in the following patients (from the literature):

- Patients with narrow-angle glaucoma.
- Patients at risk for thyrotoxicosis.
- Patients with renal impairment.
- Diabetic patients: Epinephrine has been shown to increase blood glucose levels and decrease insulin sensitivity.
- Patients with organic brain damage.
- Patients with pheochromocytoma.
- Patients with neurotic disorder.
- Patients with asthma and/or emphysema.
- Patients with Parkinson's disease.

7.5.5 Drug-Drug Interactions

From the Twinject label:
"Patients who receive epinephrine while concomitantly taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, sodium levothyroxine, and certain antihistamines, notably chlorpheniramine, tripelennamine, and diphenhydramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by betaadrenergic blocking drugs, such as propranolol. The vasoconstricting and hypertensive effects are antagonized by alpha-adrenergic blocking drugs, such as phentolamine. Ergot alkaloids and phenothiazines may also reverse the pressor effects of epinephrine,"

Additionally from the published literature:

- Sympathomimetic drugs: can cause arrhythmias.
- Alpha adrenergic receptor antagonists (alpha blockers): Can antagonize the vasoconstriction and hypertension caused by high doses of epinephrine.
- Beta adrenergic receptor antagonists (beta blockers): Can increase the pressor effect of epinephrine
- Halogenated hydrocarbon anesthetics: may induce cardiac arrhythmia.
- Monoamine oxidase (MAO) inhibitors: may result in severe, prolonged hypertension.
- Antihistamines: May potentiate the effects of epinephrine on heart rate and rhythm.
- Thyroid hormones: May potentiate the effects of epinephrine on heart rate and rhythm.
- Vasodilators: May counteract the pressor effects of epinephrine.

- Diuretic agents: May decrease the vascular response to pressor drugs or sensitize the heart to arrhythmias
- Bronchodilators: May have an additive effect.
- Antihypertensives: May decrease the effect of epinephrine.
- Digitalis glycosides: May sensitize the heart to arrhythmias.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

NA

7.6.2 Human Reproduction and Pregnancy Data

Twinject labeling (Greenstone, LLC 2010)
"Pregnancy Category C. Although there are no adequate and well-controlled studies in pregnant women, epinephrine crosses the placenta and could lead to fetal anoxia, spontaneous abortion or both. Therefore, epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus."

Additionally from the published literature, The United Kingdom (UK) Public Assessment Report (UKPAR) for an approved Adrenaline (Epinephrine) 1 in 1000 Solution for Injection product in the UK reports the following for epinephrine (**MHRA 2006**):
"Adrenaline/epinephrine usually inhibits spontaneous or oxytocin induced contractions of the pregnant human uterus and may delay the second stage of labour. In dosage sufficient to reduce uterine contractions, the drug may cause a prolonged period of uterine atony with haemorrhage. If used during pregnancy, adrenaline/epinephrine may cause anoxia to the foetus.

For this reason parenteral adrenaline/epinephrine should not be used during the second stage of labour. Adrenaline/epinephrine should only be used during pregnancy if the potential benefits justify the possible risks to the foetus. Adrenaline /epinephrine is distributed into breast milk. Breast-feeding should therefore be avoided in mothers receiving Adrenaline/Epinephrine Injection."

Mustafa (2012) in a review article of hypertension in pregnancy stated that epinephrine should not be used in obstetrics when maternal blood pressure exceeds 130/80 mmHg.

7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor has requested a pediatric waiver based on their assessment of the small pediatric population who develops septic shock. In this submission essentially no literature has been submitted on epinephrine use in the pediatric population with septic shock.

However, at the PeRC meeting 4 September 2013 it was agreed that it is important to include in the label information (or the lack of it) regarding the use of epinephrine in septic shock in the pediatric population. The PeRC Committee recommended that information from all sources be considered in order to have an appropriate label for all ages. Therefore, in the Complete Response letter a request will be included for available pediatric information from the literature.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Generally epinephrine is not known for its drug abuse potential but this reviewer did find a case report of a 19 year old man with a history of intravenous drug abuse who injected 1.1 mg of epinephrine from an over-the-counter bronchodilator inhaler. He suffered chest discomfort and palpitations with EKG changes. Also he had mild hypokalemia and hyperglycemia. He responded with fluids and nitroglycerin **(Hall).**

7.7 Additional Submissions / Safety Issues

Although epinephrine does not seem to cause the severe peripheral vasospasm that phenylephrine does, if it is injected accidently intra-arterially it can cause severe arterial vasospasm. **(Roberts)**

8 Postmarket Experience

This product, Belcher's Epinephrine Injection, USP 1:1000 mg/mL has not been marketed, nor have any other FDA-approved intravenous epinephrine products. However, intravenous epinephrine has been used as a vasopressor for over 50 years in treating hypotension associated with septic shock. The literature documents that epinephrine significantly improves systemic arterial blood pressure.

9 Appendices

9.1 Literature Review/References

Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. [NCT00148278]. Lancet. 2007 Aug 25; 370(9588):676-684.

Beck M, Clutter W et al. Enhanced Glycemic Responsiveness to Epinephrine in Insulin-dependent Diabetes Mellitus Is the Result of the Inability to Secrete Insulin. J. Clin. Invest. 1985;75: 1842-1851.

Bollaert PE, Bauer P, Audibert G, et al. Effects of epinephrine on hemodynamics and oxygen metabolism in dopamine-resistant septic shock. Chest. 1990 Oct;98(4):949-953.

Day NP, Phu NG, Bethell DP, et al. The effects of dopamine and adrenaline infusions on acidbase balance and systemic hemodynamics in severe infection. Lancet. 1996 Jul 27; 348: 219-223.

De Backer D, Creteur J, Silva E, et al. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? Crit Care Med. 2003 Jun;31(6):1659-1667.

Duranteau J, Sitbon P, Teboul JL, et al. Effects of epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock. Crit Care Med. 1999 May;27(5):893-900.

Ellenhorn Mathew J. Ellenhorn's Medical Toxicology. 2nd ed. Williams and Wilkins, 1997.

Ersoz Namik and Finestone S.C. Adrenaline-induced Pulmonary Edema and Its Treatment. Brit J Anaesth. 1971; 43: 709-712.

Ferry David et al. Epinephrine-induced myocardial infarction in a patient with angiographically normal coronary arteries. Am Ht J 1986; 111: 1193-5.

Fyfe Alistair et al. Reversible "Cardiomyopathy" After Accidental Adrenaline Overdose. Am J Cardio 1990; 67:318-9.

Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill, 2011.

Hall Alan et al. Intravenous Epinephrine Abuse. Am J Emerg Med 1987; 5: 64-65.

Illi A, Sundberg S, Ojala-Karlsson P, et al. The effect of entacapone on the disposition and hemodynamic effects of intravenous isoproterenol and epinephrine. Clin Pharmacol Ther. 1995Aug;58(2):221-227.

Karch Steven Coronary Artery Spasm Induced by Intravenous Epinephrine Overdose. Am J Emerg Med 1989; 7: 485-7.

Levy B, Bollaert PE, Charpentier C, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Med. 1997;23: 282–287.

Levy B, Gibot S, Franck P, et al. Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. Lancet. 2005a Mar;365(9462):871-875.

Levy B, Dusang B, Annane D, et al. Cardiovascular response to dopamine and early prediction of outcome in septic shock: a prospective multiple-center study. Crit Care Med. 2005c Oct;33(10):2172-2177.

Lipman J, Roux A, Kraus P. Vasoconstrictor effects of adrenaline in human septic shock. Anaesth Intensive Care. 1991 Feb;19(1):61-65.

Le Tulzo Y, Seguin P, Gacouin A, et al. Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure: a preliminary descriptive study. Intensive Care Med. 1997;23: 664–670.

Mackenzie SJ, Kapadia F, Nimmo GR, et al: Adrenaline in treatment of septic shock: Effects on haemodynamics and oxygen transport. *Intensive Care Med* 1991; 17:36–39
Moran JL, O'Fathartaigh MS, Peisach AR, et al: Epinephrine as an inotropic agent in septic shock: A dose-profile analysis. Crit Care Med 1993; 21:70–77.

Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Med. 2008;34:2226–2234.

Novey Harold et al. Alarming Reaction After Intravenous Administration of 30 ml of Epinephrine. JAMA 1969; 207: 2435-6.

Roberts James R et al. Accidental Intra-arterial Injection of Epinephrine Treated with Phentolamine. Ann Emerg Med. 1989; 18: 424-425.

Seguin P, Bellissant E, Tulzo YL, et al. Effects of epinephrine compared with the combination of dobutamine and norepinephrine on gastric perfusion in septic shock. Clin Pharmacol Ther. 2002 May;71(5):381-388.

Seguin P, Laviollo B, Guinet P, et al. Dopexamine and norepinephrine versus epinephrine on gastric perfusion in patients with septic shock: a randomized study [NCT00134212]. Crit Care. 2006 Feb;10(1):R32.

Wilson W, Lipman J, Scribante J, et al. Septic shock: does adrenaline have a role as a first-line inotropic agent? Anaesth Intensive Care. 1992 Nov;20(4):470-474.

Wutrich Y, Barraud D, Conrad M, et al. Early increase in arterial lactate concentration under epinephrine infusion is associated with a better prognosis during shock. Shock. 2010 Jul;34(1):4-9

9.2 Labeling Recommendations

The label review will be submitted separately.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting is planned.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GAIL I MORESCHI
09/19/2013

SHARI L TARGUM
09/19/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205029 **Applicant: Belcher** **Stamp Date: 12/4/12**

Drug Name: epinephrine **NDA/BLA Type: standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?		X		
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Twinject NDA 20800
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			x	

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			x	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer	Date
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GAIL I MORESCHI
01/24/2013