HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPINEPHRINE INJECTION USP safely and effectively. See full prescribing information for EPINEPHRINE INJECTION USP.

EPINEPHRINE INJECTION USP, 1 mg/mL (1:1,000) ampule for IV infusion
Initial U.S. Approval: 1939

----------INDICATIONS AND USAGE----------
Epinephrine is an alpha and beta adrenergic agonist indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. (1)

----------DOSAGE AND ADMINISTRATION----------
- Dilute epinephrine in dextrose solution prior to infusion. (2)
- Infuse epinephrine into a large vein. (2)
- Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure (2)
- Wean gradually. (2)

----------DOSAGE FORMS AND STRENGTHS----------
2 mL ampule containing 1 mg/1 mL epinephrine (1:1,000 Injection, USP). (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Correct blood volume depletion. (5.1)
- Titrate carefully while patient vital signs are continuously monitored. (5.2)
- Avoid extravasation into tissues, which can cause local necrosis. (5.3)
- Potential for pulmonary edema, which may be fatal (5.4)
- May constrict renal blood vessels and decrease urine formation. (5.5)
- May induce potentially serious cardiac arrhythmias in patients. (5.6)
- MAO inhibitors and antidepressants may prolong hypertension. (5.7)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > 1%) are headache; anxiety; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; peripheral coldness; nausea/vomiting; and/or respiratory difficulties. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Belcher Pharmaceuticals at (727) 471-0850 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Drugs that counter the pressor effects of epinephrine include alpha blockers, vasodilators such as nitrates, diuretics, and antihypertensives. (7.1)
- Drugs that potentiate the pressor effects of epinephrine include sympathomimetics, beta blockers, tricyclic antidepressants, MAO inhibitors, COMT inhibitors, clonidine, doxapram, and oxytocin. (7.2)
- Drugs that increase the arrhythmogenic potential of epinephrine include beta blockers, cyclopropane and halogenated hydrocarbon anesthetics, antihistamines, exogenous thyroid hormones, diuretics, and digitalis glycosides. (7.2)
- Potassium-depleting drugs, including corticosteroids, diuretics, and theophylline, potentiate the hypokalemic effects of epinephrine. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Epinephrine may lead to fetal anoxia, spontaneous abortion or both. (8.1)
- Avoid breast-feeding with epinephrine. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: July 2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
2.2 Recommended Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Blood Volume Replacement
5.2 Acute Hypertension
5.3 Extravasation
5.4 Pulmonary Edema
5.5 Renal Impairment
5.6 Cardiac Arrhythmias
5.7 Prolonged Hypertension
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
7.1 Epinephrine's Effects on Other Drugs
7.2 Effects of Other Drugs on Epinephrine
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
Treating Hypotension from Septic Shock with Epinephrine
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Epinephrine Injection USP, 1 mg/mL (1:1,000) is indicated to increase mean arterial blood pressure in hypotension associated with septic shock.

2 DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard any unused portion.

Dilute epinephrine in 5 percent dextrose solution or 5 percent dextrose and sodium chloride solution. These dextrose containing fluids provide protection against significant loss of potency by oxidation. **Administration in saline solution alone is not recommended.** Whole blood or plasma, if indicated to increase blood volume, should be administered separately.

Add 1 mL (1 mg) of epinephrine from its ampule to 1,000 mL of a 5 percent dextrose containing solution. Each mL of this dilution contains 1 mcg of epinephrine.

Blood volume depletion should always be corrected as fully as possible before any vasopressor is administered. When, as an emergency measure, intraaortic pressures must be maintained to prevent cerebral or coronary artery ischemia, epinephrine can be administered before and concurrently with blood volume replacement.

Whenever possible, give infusions of epinephrine into a large vein. Avoid using a catheter tie-in technique, because the obstruction to blood flow around the tubing may cause stasis and increased local concentration of the drug. Occlusive vascular diseases (for example, atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease) are more likely to occur in the lower than in the upper extremity; therefore, avoid the veins of the leg in elderly patients or in those suffering from such disorders. There is potential for gangrene in a lower extremity when infusions of catecholamine are given in an ankle vein.

To provide hemodynamic support in septic shock associated hypotension in adult patients, the suggested dosing infusion rate of intravenously administered epinephrine is 0.05 mcg/kg/min to 2 mcg/kg/min, and is titrated to achieve a desired mean arterial pressure (MAP). The dosage may be adjusted periodically, such as every 10 - 15 minutes, in increments of 0.05 mcg/kg/min to 0.2 mcg/kg/min, to achieve the desired blood pressure goal.

Continuous epinephrine infusion is generally required over several hours or days until the patient's hemodynamic status improves. The duration of perfusion or total cumulative dose cannot be predicted.

After hemodynamic stabilization, wean incrementally over time, such as by decreasing doses of epinephrine every 30 minutes over a 12- to 24-hour period.

3 DOSAGE FORMS AND STRENGTHS

2 mL clear glass ampule containing 1 mg/1 mL epinephrine as the hydrochloride in a sterile, preservative free/sulfite free solution, marked Epinephrine Injection USP, 1 mg/mL (1:1,000) *[see Dosage and Administration(2.2)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Blood Volume Replacement

Correct blood volume depletion before any vasopressor is administered.

5.2 Acute Hypertension

Titrate epinephrine infusion while monitoring vital signs. Invasive arterial blood pressure monitoring and central venous pressure monitoring are recommended. Because of varying response to epinephrine, dangerously high blood pressure may occur.

5.3 Extravasation

The infusion site should be checked frequently for free flow. Avoid extravasation of epinephrine into the tissues, to prevent local necrosis. Blanching along the course of the infused vein, sometimes without obvious extravasation, may be attributed to vasa vasorum constriction with increased permeability of the vein wall, permitting some leakage. This also may progress on rare occasions to superficial slough. Hence, if blanching occurs, consider changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

Antidote for Extravasation Ischemia: To prevent sloughing and necrosis in areas in which extravasation has taken place, infiltrate the area with 10 mL to 15 mL of saline solution containing from 5 mg to 10 mg of **phentolamine**, an adrenergic blocking agent. Use a syringe with a fine hypodermic needle, with the solution being infiltrated liberally throughout the area, which is easily identified by its cold, hard, and pallid appearance. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours.

5.4 Pulmonary Edema

There is risk of pulmonary edema because of the peripheral constriction and cardiac stimulation produced.

5.5 Renal Impairment

Intravenously administered epinephrine initially may produce constriction of renal blood vessels and decrease urine formation.

5.6 Cardiac Arrhythmias

Epinephrine may induce cardiac arrhythmias in patients, especially those patients suffering from heart disease, organic heart disease, or who are receiving drugs that sensitize the myocardium.

5.7 Prolonged Hypertension

Patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types may experience severe, prolonged hypertension when given epinephrine.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of epinephrine were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Cardiovascular disorders: tachycardia, supraventricular tachycardia, ventricular arrhythmias, myocardial ischemia, myocardial infarction, limb ischemia, pulmonary edema
Gastrointestinal disorders: Nausea, vomiting
General disorders and administrative site conditions: Chest pain, extravasation,
Metabolic: hypoglycemia, hyperglycemia, insulin resistence, hypokalemia, lactic acidosis
Nervous system disorders: Headache, nervousness, paresthesia, tremor, stroke, central nervous system bleeding
Psychiatric disorders: Excitability
Renal disorders: Renal insufficiency
Respiratory: Pulmonary edema, rales
Skin and subcutaneous tissue disorders: Diaphoresis, pallor, piloerection, skin blanching, skin necrosis with extravasation

7 DRUG INTERACTIONS

7.1 Epinephrine's Effects on Other Drugs

Antihypertensives: Epinephrine may antagonize the neuronal blockade produced by guanethidine resulting in decreased antihypertensive effect and requiring increased dosage of the latter.

7.2 Effects of Other Drugs on Epinephrine

Drugs antagonizing pressor effects

- α-blockers, such as phentolamine
- Vasodilators, such as nitrates
- Diuretics
- Antihypertensives

Drugs potentiating pressor effects

- Sympathomimetics
- β-blockers
- Tricyclic anti-depressants
- Monoamine oxidase (MAO) inhibitors
- Catechol-O-methyl transferase (COMT) inhibitors, such as entacapone
- Clonidine
- Doxapram
- Oxytocin

Drugs potentiating arrythmogenic effects

- β-blockers
- Cyclopropane or halogenated hydrocarbon anesthetics, such as halothane
- Antihistamines
- Thyroid hormones
- Diuretics
- Digitalis glycosides

Drugs potentiating hypokalemic effects

- Potassium depleting diuretics
- Corticosteroids
- Theophylline

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Epinephrine has been shown to have developmental effects in rabbits at a subcutaneous dose of 1.2 mg/kg (approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), in mice at a subcutaneous dose of 1 mg/kg (approximately 7 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), and in hamsters at a subcutaneous dose of 0.5 mg/kg (approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). Although there are no adequate and well-controlled studies in pregnant women, epinephrine crosses the placenta (but not the blood-brain barrier) and could lead to fetal anoxia, spontaneous abortion or both. Data from animal studies have shown that epinephrine interferes with ovum implantation and fetus survival in rabbits and has teratogenic potential.

8.2 Labor and Delivery

Epinephrine usually inhibits spontaneous or oxytocin induced contractions of the pregnant human uterus and may delay the second stage of labor. Avoid epinephrine during the second stage of labor. In dosage sufficient to reduce uterine contractions, the drug may cause a prolonged period of uterine atony with hemorrhage. Avoid epinephrine in obstetrics when maternal blood pressure exceeds 130/80 mmHg.

8.3 Nursing Mothers

Epinephrine is distributed into breast milk. Avoid breast-feeding in mothers receiving infusion of epinephrine.

8.4 Pediatric Use

Safety and effectiveness of epinephrine in pediatric patients with septic shock have not been established.

8.5 Geriatric Use

Clinical studies of epinephrine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Myocardial ischemia and infarction, cardiomyopathy, pulmonary edema, and renal insufficiency were observed in literature reports of accidental overdoses.

Toxic effects of overdosage can be counteracted by injection of an alpha-adrenergic blocker (such as phentolamine mesylate) and a beta-adrenergic blocker (such as propranolol). Rapid-acting vasodilators such as nitrites, or alpha-adrenergic blocking agents can be given to counteract the marked pressor effect of large doses of epinephrine causing a sharp rise in the blood pressure. Treatment of acute toxicity is mainly supportive since epinephrine is rapidly inactivated in the body.

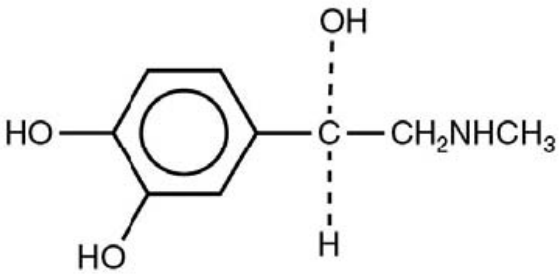
Epinephrine overdosage can also cause transient bradycardia followed by tachycardia, and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug such as propranolol.

11 DESCRIPTION

Epinephrine Injection USP, 1 mg/mL (1:1,000) is supplied as a sterile aqueous solution that is colorless and nonpyrogenic. Each milliliter contains 1 mg Epinephrine base (as the hydrochloride), Sodium Chloride 9 mg (for isotonicity), and Water for Injection, USP, qs. Contains no sulfites. May contain Hydrochloric Acid for pH adjustment.

This sterile solution is to be administered after dilution by the intravenous route. The solution contains no preservatives such as sulfites.

Epinephrine, USP is a sympathomimetic (adrenergic) agent designated chemically as 4-[1-hydroxy-2 (methylamino) ethyl]-1,2 benzenediol, a white, microcrystalline powder. It has the following structural formula:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epinephrine acts on both alpha (α)- and beta (β)-adrenergic receptors. The mechanism of the rise in blood pressure is 3-fold: a direct myocardial stimulation that increases the strength of ventricular contraction (positive inotropic action), an increased heart rate (positive chronotropic action), and peripheral vasoconstriction.

12.2 Pharmacodynamics

Following intravenous administration of epinephrine, increases in systolic blood pressure and heart rate are observed. Decreases in systemic vascular resistance and diastolic blood pressure are observed at low doses of epinephrine because of β_2-mediated vasodilation, but are overtaken by α_1-mediated peripheral vasoconstriction at higher doses leading to increase in diastolic blood pressure. The onset of blood pressure increase following an intravenous dose of epinephrine is < 5 minutes and the time to offset blood pressure response occurs within 20 min. Most vascular beds are constricted including renal, splanchnic, mucosal and skin.

12.3 Pharmacokinetics

Following intravenous injection, epinephrine is rapidly cleared from the plasma with an effective half-life of < 5 min. A pharmacokinetic steady state following continuous intravenous infusion is achieved within 10-15 min. In patients with septic shock, epinephrine displays dose-proportional pharmacokinetics in the infusion dose range of 0.03 to 1.7 mcg/kg/min.

Epinephrine is extensively metabolized with only a small amount excreted unchanged. Epinephrine is rapidly degraded to vanillylmandelic acid, an inactive metabolite, by monoamine oxidase and catechol-O-methyltransferase that are abundantly expressed in the liver, kidneys and other extraneuronal tissues. The tissues with the highest contribution to removal of circulating exogenous epinephrine are the liver (32%), kidneys (25%), skeletal muscle (20%), and mesenteric organs (12%).

Special Populations

Elderly

In a pharmacokinetic study of 45-minute epinephrine infusions given to healthy men aged 20 to 25 years and healthy men aged 60 to 65 years, the mean plasma metabolic clearance rate of epinephrine at steady state was greater among the older men (144.8 versus 78 mL/kg/min for a 14.3 ng/kg/min infusion).

Body Weight

Body weight has been found to influence epinephrine pharmacokinetics. Higher body weight was associated with a higher plasma epinephrine clearance and a lower concentration plateau.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate carcinogenesis studies have not been reported. An equivocal response of epinephrine was found when tested in Salmonella typhimurium strain TA 100 in the absence of metabolic activation system (S9) and negative in the presence of activation system (S9).

There are no data from either animal or human studies regarding potential for the impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

Epinephrine was associated with metabolic effects, decreased mesenteric, coronary and renal conductance in a sheep model of septic shock. Data from hemolysis study have shown that epinephrine at 1:1,000 dilution is non-hemolytic. Epinephrine infusion significantly increased the MAP (69 vs. 86 mmHg) and cardiac output (6.4 vs. 7.1 L/min) and decreased renal blood flow (330 vs. 247 mL/min).

14 CLINICAL STUDIES

Treating Hypotension from Septic Shock with Epinephrine

Fourteen clinical studies from the literature documented that epinephrine increases the mean arterial pressure (MAP) in patients with hypotension associated with septic shock.

16 HOW SUPPLIED/STORAGE AND HANDLING

Epinephrine Injection USP, 1 mg/mL (1:1,000) is a sterile solution containing 1 mg/1 mL epinephrine as the hydrochloride in each 2 mL clear glass ampule. Epinephrine contains no preservatives, such as sulfites. Supplied in a box of 10 ampules (NDC 62250-103-10).

Protect from light until ready to use.
Do not refrigerate. Protect from freezing.
Store at room temperature, between 20 - 25°C (68 - 77°F).
Protect from alkalis and oxidizing agents.
Solutions for intravenous use should be inspected visually for particulate matter and discoloration, whenever solution and container permit.
Do not use after the expiration date.

17 PATIENT COUNSELING INFORMATION

If possible, interrogate patients regarding any pre-existing conditions, such as heart disease or diabetes, medications that they are taking, or any known hypersensitivity to sympathomimetic drugs.

Revised: July 2014

Manufactured for:

Belcher Pharmaceuticals, LLC

Belcher Pharmaceuticals, LLC, Largo, FL 33777 USA

Manufactured by:

Sintetica SA
Via Penate 5
6850 Mendrisio, Switzerland