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 and intraocular use
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. (1.1)
- For induction and maintenance of mydriasis during intraocular surgery. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Hypotension associated with septic shock:
  - Dilute epinephrine in dextrose solution prior to infusion. (2.1)
  - Infuse epinephrine into a large vein. (2.1)
  - Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure (2.1)
  - Wean gradually. (2.1)
- Intraocular surgery:
  - Dilute 1 mL with 100 to 1000 mL of an ophthalmic irrigation fluid, for ophthalmic irrigation or intracameral injection. (2.2)

----------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)
- Undiluted ophthalmic administration: associated with corneal endothelial damage. (5.8)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > 1%) to systemically administered epinephrine 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 infusion. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: June 2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hypotension associated with septic shock

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

1.2 Induction and maintenance of mydriasis during intraocular surgery

Induction and maintenance of mydriasis during intraocular surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Hypotension associated with septic shock

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.

2.2 Induction and maintenance of mydriasis during intraocular surgery

Epinephrine must be diluted prior to intraocular use. Dilute 1 mL of epinephrine 1 mg/mL (1:1000) in 100 to 1000 mL of an ophthalmic irrigation fluid to create an epinephrine concentration of 1:100,000 to 1:1,000,000 (10 mcg/mL to 1 mcg/mL). Use the irrigating solution as needed for the surgical procedure.

After dilution in an ophthalmic irrigating fluid, epinephrine may also be injected intracamerally as a bolus dose of 0.1 mL at a dilution of 1:100,000 to 1:400,000 (10 mcg/mL to 2.5 mcg/mL).

Inspect visually for particulate matter and discoloration prior to administration. Do not use if the solution is colored or cloudy, or if it contains particulate matter.

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)]*.

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.

5.8 Injury with Undiluted Intraocular Solution

Epinephrine **must** be diluted before intraocular use. Other products of epinephrine containing sodium bisulfite have been associated with corneal endothelial damage when used in the eye at undiluted concentrations (1 mg/mL). Although this Epinephrine product contains no sulfites and is sulfite-free/preservative-free, warning is still advised [*see Dosage and Administration (2.2)*].

6 ADVERSE REACTIONS

6.1 Adverse Reactions Associated with Infusion (for Hypotension Associated with Septic Shock)

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 resistance, 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

6.2 Adverse Reactions Associated with Intraocular Use (for Mydriasis)

Epinephrine containing sodium bisulfite has been associated with corneal endothelial damage when used in the eye at undiluted concentrations (1 mg/mL). Although this Epinephrine product contains no sulfites and is sulfite-free/preservative-free, warning is still advised [*see Warnings and Precautions (5.8)*].

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

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 arrhythmogenic 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

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