

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205029Orig1s000

LABELING

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

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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 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

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

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