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 (1:1000) ampule, for intravenous, intramuscular, subcutaneous, and intraocular use

Initial U.S. Approval: 1939

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	2/2016
Indications and Usage (1.3)	10/2015
Dosage and Administration (2.1)	2/2016
Dosage and Administration (2.3)	2/2016
Dosage and Administration (2.4)	10/2015
Warnings and Precautions (5.7)	10/2015
Warnings and Precautions (5.1, 5.3, 5.4, 5.6, 5.8)	2/2016

----------INDICATIONS AND USAGE----------

Epinephrine is a non-selective alpha and beta adrenergic agonist indicated:

- To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. (1.1)
- For emergency treatment of allergic reactions (Type 1), including anaphylaxis. (1.2)
- For induction and maintenance of mydriasis during intraocular surgery. (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Hypotension associated with septic shock:
  - Dilute epinephrine in dextrose solution prior to infusion. (2.2)
  - Infuse epinephrine into a large vein. (2.2)
  - Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure (2.2)
  - Wean gradually. (2.2)
- Anaphylaxis:
  - *Adults and Children 30 kg (66 lbs) or more:* 0.3 to 0.5 mg (0.3 to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary. (2.3)
  - *Children 30 kg (66 lbs) or less:* 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary. (2.3)
- Intraocular surgery:
  - Dilute 1 mL with 100 to 1000 mL of an ophthalmic irrigation fluid, for ophthalmic irrigation or intracameral injection. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Injection solution: 1 mg/1 mL (1:1000), 2 mL single-use ampule. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Monitor patient for acute severe hypertension. (5.1)
- Avoid extravasation into tissues, which can cause local necrosis. (5.2)
- Do not inject into buttocks, digits, hands, or feet. (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 or aggravate angina pectoris, particularly in patients with underlying heart disease. (5.6)
- Patients with hyperthyroidism, Parkinson's disease, diabetes, and pheochromocytoma are at greater risk of having adverse reactions when used intravenously, intramuscularly, or subcutaneously. (5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions to systemically administered epinephrine are headache; anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; peripheral coldness; nausea/vomiting; and/or respiratory difficulties. Arrhythmias, including fatal ventricular fibrillation, rapid rises in blood pressure producing cerebral hemorrhage, and angina have occurred. (6.1, 6.2)

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, antihypertensives, and ergot alkaloids. (7)
- Drugs that potentiate the effects of epinephrine include sympathomimetics, beta blockers, tricyclic antidepressants, MAO inhibitors, COMT inhibitors, clonidine, doxapram, oxytocin, levothyroxine sodium, and certain antihistamines. (7)
- Drugs that increase the arrhythmogenic potential of epinephrine include beta blockers, cyclopropane and halogenated hydrocarbon anesthetics, quinidine, antihistamines, exogenous thyroid hormones, diuretics, and cardiac glycosides. Observe for development of cardiac arrhythmias. (7)
- Potassium-depleting drugs, including corticosteroids, diuretics, and theophylline, potentiate the hypokalemic effects of epinephrine. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Epinephrine may lead to fetal anoxia, spontaneous abortion or both. (8.1)
- Elderly patients and pregnant women may be at greater risk of developing adverse reactions when epinephrine is administered parenterally. (8.1, 8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 2/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hypotension associated with Septic Shock

Epinephrine Injection USP, 1 mg/mL (1:1000) is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

1.2 Anaphylaxis

Emergency treatment of allergic reactions (Type I), including anaphylaxis, which may result from allergic reactions to insect stings, biting insects, foods, drugs, sera, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. The signs and symptoms associated with anaphylaxis include flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with hypotension, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, airway swelling, laryngospasm, bronchospasm, pruritus, urticaria or angioedema, swelling of the eyelids, lips, and tongue.

1.3 Induction and Maintenance of Mydriasis during Intraocular Surgery

Induction and maintenance of mydriasis during intraocular surgery.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is colored or cloudy, or if it contains particulate matter. Discard any unused portion.

2.2 Hypotension associated with Septic Shock

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.

Correct blood volume depletion 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.

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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.

2.3 Anaphylaxis

Inject epinephrine intramuscularly or subcutaneously into the anterolateral aspect of the thigh. The injection may be repeated every 5 to 10 minutes as necessary. For intramuscular administration, use a needle long enough (at least 1/2 inch to 5/8 inch) to ensure the injection is administered into the muscle. Monitor the patient clinically for the severity of the allergic reaction and potential cardiac effects of the drug, with repeat doses titrated to effect. Do not administer repeated injections at the same site, as the resulting vasoconstriction may cause tissue necrosis.

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) of undiluted epinephrine administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, up to a maximum of 0.5 mg (0.5 mL) per injection, repeated every 5 to 10 minutes as necessary. Monitor clinically for reaction severity and cardiac effects.

Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) of undiluted epinephrine administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, up to a maximum of 0.3 mg (0.3 mL) per injection, repeated every 5 to 10 minutes as necessary. Monitor clinically for reaction severity and cardiac effects.

2.4 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.

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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).

3 DOSAGE FORMS AND STRENGTHS

Injection solution: 1 mg/1 mL (1:1000) epinephrine as a sterile solution in a 2 mL single-use clear glass ampule, marked Epinephrine Injection USP, 1 mg/mL (1:1000).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

When Epinephrine Injection is administered intravenously, titrate the 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.

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

5.2 Extravasation and Tissue Necrosis with Intravenous Infusion

When Epinephrine Injection is administered intravenously, 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.

5.3 Incorrect Locations of Injection for Anaphylaxis

When Epinephrine Injection is used for the treatment of anaphylaxis, the most appropriate location for administration is into the anterolateral aspect of the thigh (vastus lateralis muscle) because of its location, size, and available blood flow. Injection into (or near) smaller muscles, such as in the deltoid, is not recommended due to possible differences in absorption associated with this use.

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