EPIPen® (epinephrine) Auto-Injector 0.3 mg
EpiPen® = one dose of 0.30 mg epinephrine (USP, 1:1000, 0.3 mL)

EPIPen Jr® (epinephrine) Auto-Injector 0.15 mg
EpiPen Jr® = one dose of 0.15 mg epinephrine (USP, 1:2000, 0.3 mL)

DESCRIPTION
Each EpiPen® Auto-Injector delivers a single dose of 0.3 mg epinephrine injection, USP, 1:1000 (0.3 mL) in a sterile solution. Each EpiPen Jr® Auto-Injector delivers a single dose of 0.15 mg epinephrine injection, USP, 1:2000 (0.3 mL) in a sterile solution. The EpiPen Auto-Injector and EpiPen Jr Auto-Injector (henceforth referred to as EpiPen and EpiPen Jr Auto-Injector) each contain 2 mL epinephrine solution. Approximately 1.7 mL remains in the auto-injector after activation and cannot be used.

Each 0.3 mL in the EpiPen Auto-Injector contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabsulfite, hydrochloric acid, and water for injection. The pH range is 2.2–5.0.

Each 0.3 mL in the EpiPen Jr Auto-Injector contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabsulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2–5.0.

Epinephrine is a sympathomimetic catecholamine. Chemically, epinephrine is B-(3, 4-di hydroxyphenyl)-a-methyl-a- aminoethanol, with the following structure:

\[
\text{HO} \quad \text{C} \quad \text{H}_2 \text{NCH}_3 \quad \text{HO} \\
\text{CH}_2 \text{C}_2 \text{H}_5
\]

Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. Replace EpiPen and EpiPen Jr Auto-Injectors if the epinephrine solution appears discolored.

EpiPen and EpiPen Jr Auto-Injectors do not contain latex.

CLINICAL PHARMACOLOGY
Epinephrine is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of anaphylaxis of unknown cause (idiopathic anaphylaxis) or exercise-induced anaphylaxis. When given intramuscularly or subcutaneously it has a rapid onset and short duration of action. Epinephrine acts on both alpha and beta adrenergic receptors. Through its action on alpha adrenergic receptors, epinephrine lessens the vasodilation and increased vascular permeability that occurs during anaphylaxis, which can lead to loss of intravascular fluid volume and hypotension. Through its action on beta-adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation that helps alleviate bronchospasm, wheezing and dyspnea that may occur during anaphylaxis. Epinephrine also alleviates pruritus, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxant effects on the smooth muscle of the stomach, intestine, uterus, and urinary bladder.

INDICATIONS AND USAGE
EpiPen and EpiPen Jr Auto-Injectors are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to such causes as foods (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic tests (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. EpiPen and EpiPen Jr Auto-Injectors are intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Selection of the appropriate dosage strength is determined according to patient body weight (see DOSAGE AND ADMINISTRATION section).

Such reactions may occur within minutes after exposure to the causative agent. The signs and symptoms of anaphylaxis may include flushing, apprehension, syncope, tachycardia, tachycardia, urticaria, angioedema, throat or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

EpiPen and EpiPen Jr Auto-Injectors are intended for immediate self-administration as emergency supportive therapy only and are not a substitute for immediate medical care.

CONTRAINDICATIONS
There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS
EpiPen and EpiPen Jr Auto-Injectors should only be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK. Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis.

Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Treatment should be directed at vasodilation in addition to further treatment of anaphylaxis (see ADVERSE REACTIONS).

Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection.

DO NOT INJECT INTRAVENTRICULARLY. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can control the hypotension and to inform the healthcare provider in the emergency room of the location of the accidental injection.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which epinephrine should be used. It must be clearly determined that the patient is at risk of future anaphylaxis, since the following risks may be associated with epinephrine administration (see DOSAGE and ADMINISTRATION).

Epinephrine should be used with caution in patients who have cardiac arrhythmias, coronary artery disease or other heart disease, hypertension, or in patients who are on drugs that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, or quinidine, or other anti-arrhythmics. In such patients, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.

Some patients may be at greater risk of developing adverse reactions after epinephrine administration. These include: hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, or individuals with existing coronary artery or organic heart disease, hypertension, or in patients who are on drugs that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, or quinidine, or other anti-arrhythmics. In such patients, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias.
Epinephrine may produce symptoms and signs that include an increase in heart rate, the sensation of a more forceful heartbeat, palpitations, sweating, nausea, vomiting, difficulty breathing, pallor, dizziness, weakness or shakiness, headache, apprehension, nervousness, or anxiety. These symptoms and signs usually subside rapidly, especially if the test is quiet and recumbent. Patients with hypertension or hyperthyroidism may develop more severe or persistent effects, and patients with coronary artery disease could experience angina. Patients may develop increased blood glucose levels following epinephrine administration. Patients with Parkinson’s disease may notice a temporary worsening of symptoms.

In case of accidental injection, the patient should be advised to immediately go to the emergency room for treatment. Since the epinephrine in the EpiPen Auto-Injector is a strong vasoconstrictor when injected into the digits, hands or feet, treatment should be directed at vasodilation if there is such an inadvertent administration to these areas (see ADVERSE REACTIONS).

The carrier tube is not waterproof. The blue safety seal helps prevent accidental injection and should be kept on until it will be used.

(3) Drug Interactions

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 tricylic antidepressants, monoamine oxidase inhibitors, levophyoxine sodium, and certain antihistamines, notably chlorpheniramine, tripelennamine and diphenhydramine.

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

(4) Carcinogenesis, Mutagenesis, Impairment of Fertility

Epinephrine and other sympathomimetics have been shown to have mutagenic potential in vitro and to be an oxidative mutagen in a WP2 bacterial reverse mutation assay. Epinephrine had a moderate degree of mutagenicity, as measured by the DNA Repair test with B. subtilis (REC) assay, but was not mutagenic in the Salmonella bacterial reverse mutation assay.

Studies of epinephrine after repeated exposure in animals to evaluate the carcinogenic and mutagenic potential or the effects on fertility or reproduction have not been conducted. This should not prevent the use of epinephrine under the conditions noted under INDICATIONS AND USAGE.

(5) Usage in Pregnancy

Pregnancy Category C: There is no study on the acute effect of epinephrine on pregnancy. Epinephrine has been shown to have developmental effects when administered subcutaneously in rabbits at a dose of 1.2 mg/kg daily for two to three days (approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m² basis) and in hamsters at a subcutaneous dose of 0.5 mg/kg daily for 10 days (approximately 7 times the maximum daily subcutaneous or intramuscular dose on a mg/m² basis) and in hamsters at a subcutaneous dose of 0.5 mg/kg daily for 10 days (approximately 7 times the maximum daily subcutaneous or intramuscular dose on a mg/m² basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg daily for 10 days (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m² basis). Although, there are no adequate and well-controlled studies in pregnant women, epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known if epinephrine passes into breast milk.

ADVERSE REACTIONS

Adverse reactions to epinephrine include tachycardia; hypotension; weakness; dizziness; flushing; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine but are more likely to occur in patients with hypertension or hyperthyroidism. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or certain drugs (see PRECAUTIONS, Drug Interactions). In blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. The potential for epinephrine to produce these effects may also contraindicate its use in an acute life-threatening allergic reaction.

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area (see WARNINGS). Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoaesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

OVERDOSAGE

Epinephrine is rapidly inactivated in the body and treatment following overdose with epinephrine is primarily supportive. If necessary, pressor effects may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking drugs. If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug.

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients.

Overdosage may also result in pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Treatment consists of a rapidly acting alpha-adrenergic blocking drug and/or respiratory support.

Epinephrine overdose may 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 (ventricular tachycardia may occur less than 1 second after injection). Treatment of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-blocking drug such as propranolol.

Overdose sometimes results in extreme pallor and coldness of the skin, metabolic acidosis and convulsions. Supportive and protective measures must be taken in such situations.

DOSE AND ADMINISTRATION

EpiPen or EpiPen Jr Auto-Injector prescribers should ensure that the patient or caregiver understands the indications and use of this product. An healthcare provider should review the patient instructions and operation of the EpiPen or EpiPen Jr Auto-Injector, in detail, with the patient or caregiver. Injet EpiPen or EpiPen Jr intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. See detailed Directions for Use on the accompanying Patient Instructions.

Selection of the appropriate dosage strength is determined according to patient body weight.

EpiPen Auto-Injector delivers 0.3 mg epinephrine injection (0.3 mL, 1:1000) and is intended for patients who weigh 30 kg or more (approximately 66 pounds or more).

EpiPen Jr Auto-Injector delivers 0.15 mg epinephrine injection (0.3 mL, 1:2000) and is intended for patients who weigh 15 to 30 kg (33 – 66 pounds).

Each EpiPen or EpiPen Jr Auto-Injector contains a single dose of epinephrine. Since the doses of epinephrine delivered from EpiPen or EpiPen Jr Auto-Injectors are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are desired. The prescriber should carefully assess each patient to determine the most appropriate dose of epinephrine, recognizing the life-threatening nature of the reactions for which this drug is indicated. With severe persistent anaphylaxis, repeat injections with an additional EpiPen Auto-Injector may be necessary.

Patients should be instructed to periodically visually inspect the epinephrine solution for particulate matter and discoloration. If the solution contains particulate matter or develops a pinkish or brown color, the patient should immediately contact their physician for a new prescription. Such changes indicate that the effectiveness of the drug product may be decreased.

HOW SUPPLIED

EpiPen Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) are available in individual cartons, NDC 49502-500-01, and as EpiPen 2-Pak®, NDC 49502-500-02, a pack that contains two EpiPen Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) and one EpiPen Auto-Injector trainer device.

EpiPen Jr Auto-Injectors (epinephrine injection, USP, 1:2000, 0.3 mL) are available in individual cartons, NDC 49502-501-01, and as EpiPen Jr 2-Pak®, NDC 49502-501-02, a pack that contains two EpiPen Jr Auto-Injectors (epinephrine injections, USP, 1:2000, 0.3 mL) and one EpiPen Auto-Injector trainer device.

EpiPen 2-Pak® and EpiPen Jr 2-Pak® also includes an S-clip to clip two cases together. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°C–30°C (59°F–86°F) (See USP Controlled Room Temperature). Do not refrigerate. Protect from light. Contains no latex.

Rx only.

MANUFACTURED FOR Mylan Specialty L.P., Basking Ridge, NJ 07920, USA
by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company

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