

"פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו ב- יוני 2017"

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Name of the medicinal product

EPIPEN

EPIPEN JR

Qualitative and quantitative composition

EPIPEN: Per 0.3 ml:

<u>Active ingredient</u>	<u>Quantity / Unit</u>
Adrenaline (Epinephrine)	0.3 mg
Excipients with known effect: Sodium metabisulfite 0.5 mg/dose, sodium chloride 1.8 mg/dose.	
For a full list of excipients, see section 11	

EPIPEN JR: Per 0.3 ml:

<u>Active ingredient</u>	<u>Quantity / Unit</u>
Adrenaline (Epinephrine)	0.15 mg
Excipients with known effect: Sodium metabisulfite 0.5 mg/dose, sodium chloride 1.8 mg/dose.	
For a full list of excipients, see section 11	

Pharmaceutical form

Solution for injection in an auto-injector (prefilled, disposable automatic injection device) for intramuscular use. Clear and colourless solution.

1 INDICATIONS AND USAGE

EpiPen and EpiPen Jr are indicated in the emergency treatment of severe allergic reactions (Type I) including anaphylaxis to stinging insects (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 testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

EpiPen and EpiPen Jr 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.

Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready 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 are intended for immediate administration as emergency supportive therapy only and are not a substitute for immediate medical care.

2 DOSAGE AND ADMINISTRATION

Selection of the appropriate dosage strength (EpiPen 0.3 mg or EpiPen Jr 0.15 mg) is determined according to patient body weight.

- Patients greater than or equal to 30 kg: EpiPen 0.3 mg
- Patients 15 to 30 kg: EpiPen Jr 0.15 mg

Inject EpiPen or EpiPen Jr intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary. Instruct caregivers of young children who are prescribed an EpiPen or EpiPen Jr and who may be uncooperative and kick or move during an injection to hold the leg firmly in place and limit movement prior to and during an injection [*see Warnings and Precautions (5.2)*].

Each EpiPen or EpiPen Jr contains a single dose of epinephrine for single-use injection. Since the doses of epinephrine delivered from EpiPen or EpiPen Jr are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are deemed necessary.

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 or EpiPen Jr may be necessary. More than two sequential doses of epinephrine should only be administered under direct medical supervision [*see Warnings and Precautions (5.1)*].

The epinephrine solution in the clear window of the EpiPen Auto-Injector should be inspected visually for particulate matter and discoloration. Epinephrine is light sensitive and should be stored in the carrier tube provided to protect it from light [*see How Supplied/Storage and Handling (16.2)*].

3 DOSAGE FORMS AND STRENGTHS

- EpiPen: Injection, 0.3 mg/0.3 mL (0.3 mL, 1:1000) epinephrine injection
- EpiPen Jr: Injection, 0.15 mg/0.3 mL, (0.3 mL 1:2000) epinephrine injection,

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Emergency Treatment

EpiPen and EpiPen Jr are intended for immediate administration as emergency supportive therapy and are not intended as a substitute for immediate medical care. **In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care.** More than two sequential doses of epinephrine should only be administered under direct medical supervision [*see Indications and Usage (1), Dosage and Administration (2)*]

5.2 Injection-Related Complications

EpiPen and EpiPen Jr should **only** be injected into the anterolateral aspect of the thigh [*see Dosage and Administration (2)*]

- **Do not inject intravenously.** Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.
- **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. Additionally, injection into the buttock has been associated with Clostridial infections (gas gangrene). Cleansing with alcohol does not kill bacterial spores, and therefore, does not lower this risk.
- **Do not inject into digits, hands or feet.** 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. 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. Treatment of such inadvertent administration should consist of vasodilation, in addition to further appropriate treatment of anaphylaxis [*see Adverse Reactions (6)*].
- **Hold leg firmly during injection.** Lacerations, bent needles, and embedded needles have been reported when EpiPen and EpiPen Jr have been injected into the thigh of young children who are uncooperative and kick or move during an injection. To minimize the risk of injection related injury when administering EpiPen to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

To be completed, it is necessary to hold firmly the injection in place for 3 seconds

5.3 Serious Infections at the Injection Site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. *Clostridium* spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce presence of bacteria on the skin, alcohol cleansing does not kill *Clostridium* spores. To decrease the risk of *Clostridium* infection, do not inject EpiPen into the buttock [*see Warnings and Precautions (5.2)*]. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

5.4 Allergic Reactions Associated with Sulfite

The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons.

The alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

5.5 Disease Interactions

Some patients may be at greater risk for developing adverse reactions after epinephrine administration. Despite these concerns, it should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

- **Patients with Heart Disease**

Epinephrine should be administered with caution to patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias [*see Drug Interactions (7) and Adverse Reactions (6)*].

- **Other Patients and Diseases**

Epinephrine should be administered with caution to patients with hyperthyroidism, diabetes, elderly individuals, and pregnant women. Patients with Parkinson's disease may notice a temporary worsening of symptoms.

6 ADVERSE REACTIONS

Due to the lack of randomized, controlled clinical trials of epinephrine for the treatment of anaphylaxis, the true incidence of adverse reactions associated with the systemic use of epinephrine is difficult to determine. Adverse reactions reported in observational trials, case reports, and studies are listed below.

Common adverse reactions to systemically administered epinephrine include anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; 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 [*see Warnings and Precautions (5.5)*].

Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs [*see Warnings and Precautions (5.5) and Drug Interactions (7)*].

Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see Warnings and Precautions (5.5)*].

Angina may occur in patients with coronary artery disease [*see Warnings and Precautions (5.5)*].

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected

area [*see Warnings and Precautions (5.2)*].

Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

Lacerations, bent needles, and embedded needles have been reported when EpiPen has been injected into the thigh of young children who are uncooperative and kick or move during the injection [*see Warning and Precautions (5.2)*].

Injection into the buttock has resulted in cases of gas gangrene [*see Warnings and Precautions (5.2)*].

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported following epinephrine injection, including EpiPen, in the thigh [*see Warnings and Precautions (5.3)*].

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>).

7 DRUG INTERACTIONS

Patients who receive epinephrine while concomitantly taking cardiac glycosides, diuretics, or anti-arrhythmics should be observed carefully for the development of cardiac arrhythmias [*see Warnings and Precautions (5.5)*].

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripeleminamine, 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well controlled studies of the acute effect of epinephrine in pregnant women.

Epinephrine was teratogenic in rabbits, mice and hamsters. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (fetal anoxia, spontaneous abortion, or both).

Epinephrine has been shown to have teratogenic effects when administered subcutaneously in rabbits at approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal dose of 1.2 $\text{mg}/\text{kg}/\text{day}$ for two to three days), in mice at approximately 7 times the maximum daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 1 $\text{mg}/\text{kg}/\text{day}$ for 10 days), and in hamsters at approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 $\text{mg}/\text{kg}/\text{day}$ for 4 days).

These effects were not seen in mice at approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a subcutaneous maternal dose of 0.5 $\text{mg}/\text{kg}/\text{day}$ for 10 days).

8.3 Nursing Mothers

It is not known whether epinephrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when EpiPen is administered to a nursing woman.

8.4 Pediatric Use

EpiPen or EpiPen Jr may be administered to pediatric patients at a dosage appropriate to body weight [*see Dosage and Administration (2)*]. Clinical experience with the use of epinephrine suggests that the adverse reactions seen in children are similar in nature and extent to those both expected and reported in adults. Since the doses of epinephrine delivered from EpiPen and EpiPen Jr are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are deemed necessary.

8.5 Geriatric Use

Clinical studies for the treatment of anaphylaxis have not been performed in subjects aged 65 and over to determine whether they respond differently from younger subjects. However, other reported clinical experience with use of epinephrine for the treatment of anaphylaxis has identified that geriatric patients may be particularly sensitive to the effects of epinephrine. Therefore, EpiPen should be administered with caution in elderly individuals, who may be at greater risk for developing adverse reactions after epinephrine administration [*see Warnings and Precautions (5.5), Overdosage (10)*].

10 OVERDOSAGE

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 rapidly acting vasodilators or alpha-adrenergic blocking drugs and/or respiratory support.

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.

Overdosage sometimes results in extreme pallor and coldness of the skin, metabolic acidosis, and kidney failure. Suitable corrective measures must be taken in such situations.

11 DESCRIPTION

EpiPen (epinephrine injection) 0.3 mg and EpiPen Jr (epinephrine injection) 0.15 mg are auto-injectors and combination products containing drug and device components.

Each EpiPen Auto-Injector, 0.3 mg delivers a single dose of 0.3 mg epinephrine from epinephrine injection, USP 1:1000 (0.3 mL) in a sterile solution.

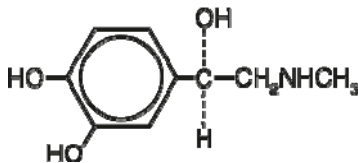
Each EpiPen Jr Auto-Injector, 0.15 mg delivers a single dose of 0.15 mg epinephrine from epinephrine injection, USP 1:2000 (0.3 mL) in a sterile solution.

The EpiPen and EpiPen Jr each contain 2 mL epinephrine solution. Approximately 1.7 mL remains in the auto-injector after activation, but is not available for future use, and should be discarded.

Each 0.3 mL in the EpiPen Auto-Injector contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 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 metabisulfite, 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 (-)-3,4-Dihydroxy- α -[(methylamino)methyl]benzyl alcohol with the following structure:



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 if the

epinephrine solution appears discolored (pinkish or brown color), cloudy, or contains particles.

Thoroughly review the patient instructions and operation of EpiPen or EpiPen Jr with patients and caregivers prior to use

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epinephrine acts on both alpha- and beta-adrenergic receptors.

12.2 Pharmacodynamics

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 and helps alleviate bronchospasm, wheezing and dyspnea that may occur during anaphylaxis.

Epinephrine also alleviates pruritus, urticaria, and angioedema and may relieve gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus and urinary bladder.

When given intramuscularly, epinephrine has a rapid onset and short duration of action.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of epinephrine have not been conducted.

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro* and to be an oxidative mutagen in a *WP2* bacterial reverse mutation assay.

Epinephrine was positive in the DNA Repair test with *B. subtilis* (REC) assay, but was not mutagenic in the *Salmonella* bacterial reverse mutation assay.

The potential for epinephrine to impair fertility has not been evaluated.

This should not prevent the use of epinephrine under the conditions noted under *Indications and Usage (1)*.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EpiPen Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) are available as EpiPen 2-Pak[®], 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 injections, USP, 1:2000, 0.3 mL) are available as EpiPen Jr 2-Pak[®], 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 include an S-clip to clip two carrier tubes together.
Rx only

EpiPen Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) are available as EpiPen single pack, a pack that contains one EpiPen Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL).

EpiPen Jr Auto-Injectors (epinephrine injections, USP, 1:2000, 0.3 mL) are available as EpiPen Jr single pack, a pack that contains one EpiPen Jr Auto-Injectors (epinephrine injections, USP, 1:2000, 0.3 mL).

16.2 Storage and Handling

Protect from light. Epinephrine is light sensitive and should be stored in the carrier tube provided to protect it from light. Store below 25 ° C. Do not refrigerate. Before using, check to make sure the solution in the auto-injector is clear and colorless. Replace the auto-injector if the solution is discolored (pinkish or brown color), cloudy, or contains particles.

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each EpiPen Auto-Injector carton.

Manufactured for Mylan Specialty L.P., Morgantown, WV 26505, U.S.A. by Meridian Medical Technologies, Inc., Columbia, MD 21046, U.S.A., a Pfizer company

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