1. NAME OF THE MEDICINAL PRODUCT

EPINEPHRINE INJECTION MYLAN 0.3 MG

EPINEPHRINE INJECTION MYLAN JR 0.3 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EPINEPHRINE INJECTION MYLAN 0.3 MG: Per 0.3 mL:

Active ingredient	**Quantity / Unit**
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 12.

EPINEPHRINE INJECTION MYLAN JR 0.15 MG: Per 0.3 mL:

Active ingredient	**Quantity / Unit**
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 12.

Pharmaceutical form

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

3. INDICATIONS AND USAGE

Epinephrine Injection Mylan and Epinephrine Injection Mylan 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.

Epinephrine Injection Mylan and Epinephrine Injection Mylan 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.

Epinephrine Injection Mylan and Epinephrine Injection Mylan Jr are intended for immediate administration as emergency supportive therapy only an Epinephrine Injection Mylan and Epinephrine Injection Mylan Jr d are not a substitute for immediate medical care.

4. DOSAGE AND ADMINISTRATION

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

- Patients greater than or equal to 30 kg: Epinephrine Injection Mylan 0.3 mg
- Patients 15 to 30 kg: Epinephrine Injection Mylan Jr 0.15 mg

Inject Epinephrine Injection Mylan or Epinephrine Injection Mylan Jr intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary. Instruct caregivers of young children who are prescribed an Epinephrine Injection Mylan or Epinephrine Injection Mylan Jr 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 (7.2)*].

Each Epinephrine Injection Mylan or Epinephrine Injection Mylan Jr contains a single dose of epinephrine for single-use injection. Since the doses of epinephrine delivered from Epinephrine Injection Mylan or Epinephrine Injection Mylan 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 Epinephrine Injection Mylan or Epinephrine Injection Mylan Jr may be necessary. More than two sequential doses of epinephrine should only be administered under direct medical supervision [*see Warnings and Precautions (7.1)*].

The epinephrine solution in the clear window of the Epinephrine Injection Mylan 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 (15.2)*].

5. DOSAGE FORMS AND STRENGTHS

- Epinephrine Injection Mylan: Injection, 0.3 mg/0.3 mL epinephrine injection, USP, pre-filled auto-injector
- Epinephrine Injection Mylan Jr: Injection, 0.15 mg/0.3 mL epinephrine injection, USP, pre-filled auto-injector

6. CONTRAINDICATIONS

None

7. WARNINGS AND PRECAUTIONS

7.1 Emergency Treatment

Epinephrine Injection Mylan and Epinephrine Injection Mylan 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 (3), Dosage and Administration (4)*].

7.2 Injection-Related Complications

Epinephrine Injection Mylan and Epinephrine Injection Mylan Jr should **only** be injected into the anterolateral aspect of the thigh [*see Dosage and Administration (4)*].

- **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 (8)*].
- **Hold leg firmly during injection.** Lacerations, bent needles, and embedded needles have been reported when Epinephrine Injection Mylan and Epinephrine Injection Mylan 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 Epinephrine Injection Mylan to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

It is necessary to hold firmly the injection in place for 3 seconds.

7.3 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 Epinephrine Injection Mylan into the buttock [see *Warnings and Precautions (***7***.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.

7.4 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.

7.5 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 Epinephrine Injection Mylan or Epinephrine Injection Mylan 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 (*9*) and Adverse Reactions (*8*)*].

- 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.

8. 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 (*7.5*)*].

Cardiovascular Reactions

- Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs [*see Warnings and Precautions (*7.5*) and Drug Interactions (*9*)*].

- Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see Warnings and Precautions (*7.5*)*].

- Angina may occur in patients with coronary artery disease [*see Warnings and Precautions (*7.5*)*].

- Rare cases of stress cardiomyopathy have been reported in patients treated with epinephrine.

Reactions from Accidental Injection and/or Improper Technique

- Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area [*see Warnings and Precautions (*7.2*)*].

- Adverse reactions 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 Epinephrine Injection Mylan has been injected into the thigh of young children who are uncooperative and kick or move during the injection [*see Warning and Precautions (*7.2*)*].

- Injection into the buttock has resulted in cases of gas gangrene [*see Warnings and Precautions*

(7.2)].

Skin and Soft Tissue Infections

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 Epinephrine Injection Mylan, in the thigh [*see Warnings and Precautions (7.3)*].

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: https://sideeffects.health.gov.il

9. DRUG INTERACTIONS

Cardiac Glycosides, Diuretics, and Anti-arrhythmics

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 (7.5)*].

Antidepressants, Monoamine Oxidase Inhibitors, Levothyroxine, and Antihistamines

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

Beta-Adrenergic Blockers

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta- adrenergic blocking drugs, such as propranolol.

Alpha-Adrenergic Blockers

The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha- adrenergic blocking drugs, such as phentolamine.

Ergot Alkaloids

Ergot alkaloids may also reverse the pressor effects of epinephrine.

10. USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

There are no adequate and well controlled studies of the acute effect of epinephrine in pregnant women. In animal reproductive studies, epinephrine administered by the subcutaneous route to rabbits, mice, and hamsters during the period of organogenesis was teratogenic at doses 7 times and higher than the maximum recommended human intramuscular and subcutaneous dose on a mg/m^2 basis. Epinephrine is the first -line medication of choice for the treatment of anaphylaxis during pregnancy in humans. Epinephrine should be used for treatment of anaphylaxis during pregnancy in the same manner as it is used in non- pregnant patients.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease -associated maternal and embryo/fetal risk:

During pregnancy, anaphylaxis can be catastrophic and can lead to hypoxic-ischemic encephalopathy and permanent central nervous system damage or death in the mother and, more commonly, in the fetus or neonate. The prevalence of anaphylaxis occurring during pregnancy is reported to be approximately 3 cases per 100,000 deliveries.

Management of anaphylaxis during pregnancy is similar to management in the general population. Epinephrine is the first line -medication of choice for treatment of anaphylaxis; it should be used in the same manner in pregnant and non-pregnant patients. In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care.

Data

Animal Data

In an embryofetal development study with rabbits dosed during the period of organogenesis, epinephrine was shown to be teratogenic (including gastroschisis and embryonic lethality) at doses approximately 40 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at a maternal subcutaneous dose of 1.2 mg/kg/day for two to three days)

In an embryofetal development study with mice dosed during the period of organogenesis, epinephrine was shown to be teratogenic (including embryonic lethality) at doses approximately 8 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at maternal subcutaneous dose of 1 mg/kg/day for 10 days). These effects were not seen in mice at approximately 4 times the maximum recommended daily intramuscular or subcutaneous dose. (on a mg/m^2 basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

Epinephrine Injection MylanIn an embryofetal development study with hamsters dosed during the period of organogenesis, from gestation days 7 to 10, epinephrine was shown to be teratogenic at doses approximately 7 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 mg/kg/day).

10.2 Lactation

Risk Summary

There is no information on the presence of epinephrine in human milk, the effects on breastfed, infants, or the effects on milk production. Epinephrine is the first line -medication of choice for treatment of anaphylaxis; it should be used in the same manner in breastfeeding and non-breastfeeding patients.

10.3 Pediatric Use

Epinephrine Injection Mylan or Epinephrine Injection Mylan Jr may be administered to pediatric patients at a dosage appropriate to body weight [*see Dosage and Administration (4)*]. 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 Epinephrine Injection Mylan and Epinephrine Injection Mylan Jr are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are deemed necessary.

10.4 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, Epinephrine Injection Mylan 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 (7.5), Overdosage (11)*].

11. 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.

12. DESCRIPTION

Epinephrine Injection Mylan (epinephrine injection, USP) 0.3 mg and Epinephrine Injection Mylan Jr (epinephrine injection, USP) 0.15 mg are single-dose auto-injectors and combination products containing drug and device components.

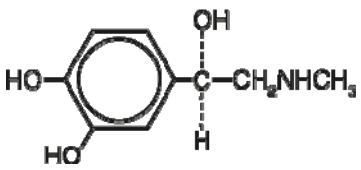
Each Epinephrine Injection Mylan Auto-Injector, 0.3 mg delivers a single dose of 0.3 mg epinephrine from epinephrine injection, USP 0.3 mg/0.3 mL in a sterile solution.

Each Epinephrine Injection Mylan Jr Auto-Injector, 0.15 mg delivers a single dose of 0.15 mg epinephrine from epinephrine injection, USP 0.15 mg/0.3 mL in a sterile solution.

Epinephrine Injection MylanEpinephrine Injection Mylan Jr
Each 0.3 mL in the Epinephrine Injection Mylan 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 Epinephrine Injection Mylan 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 Epinephrine Injection Mylan and Epinephrine Injection Mylan Jr if the epinephrine solution appears discolored (pinkish or brown color), cloudy, or contains particles.

Thoroughly review the patient instructions and operation of Epinephrine Injection Mylan or Epinephrine Injection Mylan Jr with patients and caregivers prior to use.

13. CLINICAL PHARMACOLOGY

13.1 Mechanism of Action
Epinephrine acts on both alpha- and beta-adrenergic receptors.

13.2 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 subcutaneously or intramuscularly, epinephrine has a rapid onset and short duration of action.

14. NONCLINICAL TOXICOLOGY

14.1 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*. Epinephrine was positive in the *Salmonella* bacterial reverse mutation assay, positive in the mouse lymphoma assay, and negative in the *in vivo* micronucleus assay. Epinephrine is an oxidative mutagen based on the *E. coli* WP2 Mutoxitest bacterial reverse mutation assay. This should not prevent the use of epinephrine where indicated *[see Indications and Usage (3)]*.
The potential for epinephrine to impair reproductive performance has not been evaluated, but epinephrine has been shown to decrease implantation in female rabbits dosed subcutaneously with 1.2 mg/kg/day (40-fold the highest human intramuscular or subcutaneous daily dose) during gestation days 3 to 9.

15. HOW SUPPLIED/STORAGE AND HANDLING

15.1 How Supplied

Epinephrine Injection Mylan Auto-Injectors (epinephrine injections, USP 0.3 mg/0.3 mL) are available as Epinephrine Injection Mylan 2-Pak, a pack that contains two Epinephrine Injection Mylan Auto-Injectors (epinephrine injections, USP 0.3 mg/0.3 mL) and one Epinephrine Injection Mylan Auto-Injector trainer device.

Epinephrine Injection Mylan Jr Auto-Injectors (epinephrine injections, USP 0.15 mg/0.3 mL) are available as Epinephrine Injection Mylan Jr 2-Pak, a pack that contains two Epinephrine Injection Mylan

Jr Auto-Injectors (epinephrine injections, USP 0.15 mg/0.3 mL) and one Epinephrine Injection Mylan Auto-Injector trainer device.

Epinephrine Injection Mylan 2-Pak and Epinephrine Injection Mylan Jr 2-Pak also include an S-clip to clip two carrier tubes together.
Epinephrine Injection Mylan Auto-Injectors (epinephrine injections, USP 0.3 mg/0.3 mL) are available as Epinephrine Injection Mylan single pack, a pack that contains one Epinephrine Injection Mylan Auto-Injectors (epinephrine injections, USP 0.3 mg/0.3 mL).

Epinephrine Injection Mylan Jr Auto-Injectors (epinephrine injections, USP 0.15 mg/0.3 mL) are available as Epinephrine Injection Mylan Jr single pack, a pack that contains one Epinephrine Injection Mylan Jr Auto-Injectors (epinephrine injections, USP 0.15 mg/0.3 mL).

15.2 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.
- Properly dispose all used, unwanted or expired Epinephrine Injection Mylan and Epinephrine Injection Mylan Jr auto-injectors.

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each Epinephrine Injection Mylan 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.

License Holder: Trupharm Marketing 1985, P.O.B. 8105, Nethanya, Israel

Registration Number: Epinephrine Injection Mylan: 161 59 35821 00, Epinephrine Injection Mylan Jr: 161 58 35820 00

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