

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**019430Orig1s061**

*Trade Name:* EpiPen and EpiPen Jr. Auto-Injector,  
0.3mg and 0.15 mg

*Generic or Proper Name:* epinephrine injection

*Sponsor:* Mylan Specialty L.P.

*Approval Date:* May 18, 2016

*Indication:* This supplemental new drug application provides for revisions to the labeling for EpiPen and EpiPen Jr.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 019430Orig1s061

### CONTENTS

<b>Reviews / Information Included in this NDA Review.</b>
---

<b>Approval Letter</b>	<b>X</b>
<b>Other Action Letters</b>	
<b>Labeling</b>	<b>X</b>
<b>REMS</b>	
<b>Summary Review</b>	
<b>Officer/Employee List</b>	
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	
<b>Medical Review(s)</b>	<b>X</b>
<b>Chemistry Review(s)</b>	<b>X</b>
<b>Environmental Assessment</b>	
<b>Pharmacology Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Microbiology Review(s)</b>	
<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	
<b>Other Reviews</b>	
<b>Risk Assessment and Risk Mitigation Review(s)</b>	
<b>Proprietary Name Review(s)</b>	
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019430Orig1s061**

**APPROVAL LETTER**



NDA 19430/S-061

**SUPPLEMENT APPROVAL**

Mylan Specialty L.P.  
791 Chestnut Ridge Road  
P. O. Box 4310  
Morgantown, WV 26504-4310

Attention: S. Wayne Talton  
Head, Global Regulatory Science and Operations

Dear Mr. Talton:

Please refer to your Supplemental New Drug Application (sNDA) dated March 4, 2016, received March 4, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EpiPen and EpiPen Jr. (epinephrine injection) Auto-Injector, 0.3mg and 0.15 mg.

We also refer to our letter dated February 5, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for EpiPen and EpiPen Jr (epinephrine injection). This information pertains to reports of lacerations and embedded needles after epinephrine injection and post-marketing adverse event reports of serious infection (e.g. *Clostridium perfringens*) at the injection site following epinephrine injection for anaphylaxis.

This supplemental new drug application provides for revisions to the labeling for EpiPen and EpiPen Jr. consistent with our February 5, 2016, letter and the changes agreed upon in our March 24, and 31, and April 15, 2016, correspondences, and changes to the carton and container labeling to incorporate USP information and revised instructions for use.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert, text for the patient information and instructions for use, and text for the trainer instructions for use, with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 19430/S-061.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager for Safety, at (301) 796-1226.

Sincerely,

*{See appended electronic signature page}*

Sally Seymour, MD  
Deputy Director for Safety  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling  
Carton and Container Labeling

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SALLY M SEYMOUR  
05/18/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019430Orig1s061**

**LABELING**



## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPIPEN® and EPIPEN Jr® safely and effectively. See full prescribing information for EPIPEN and EPIPEN Jr.

EPIPEN® (epinephrine injection, USP), Auto-Injector 0.3 mg, EPIPEN Jr® (epinephrine injection, USP) Auto-Injector 0.15 mg, for intramuscular or subcutaneous use

Initial U.S. Approval: 1939

### RECENT MAJOR CHANGES

- Dosage and Administration (2) 05/2016
- Warnings and Precautions (5.2, 5.3) 05/2016

### INDICATIONS AND USAGE

EpiPen and EpiPen Jr contain epinephrine, a non-selective alpha and beta-adrenergic receptor agonist, indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis. (1)

### DOSAGE AND ADMINISTRATION

- Patients greater than or equal to 30 kg (66 lbs): EpiPen 0.3 mg (2)
- Patients 15 to 30 kg (33 lbs to 66 lbs): EpiPen Jr 0.15 mg (2)

Inject EpiPen and EpiPen Jr intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Each device is a single-use injection. (2)

### DOSAGE FORMS AND STRENGTHS

- EpiPen: Injection, 0.3 mg: 0.3 mg/0.3 mL epinephrine, USP, pre-filled auto-injector (3)
- EpiPen Jr: Injection, 0.15 mg: 0.15 mg/0.3 mL epinephrine, USP, pre-filled auto-injector (3)

### CONTRAINDICATIONS

None (4)

### WARNINGS AND PRECAUTIONS

- In conjunction with use, seek immediate medical or hospital care. (5.1)
- Do not inject intravenously, into buttock, or into digits, hands, or feet. (5.2)
- To minimize the risk of injection related injury, instruct caregivers to

hold the child's leg firmly in place and limit movement prior to and during injection when administering to young children. (5.2)

- Rare cases of serious skin and soft tissue infections have been reported following epinephrine injection. Advise patients to seek medical care if they develop signs or symptoms of infection. (5.3)
- The presence of a sulfite in this product should not deter use. (5.4)
- Administer with caution in patients with heart disease; may aggravate angina pectoris or produce ventricular arrhythmias. (5.5)

### ADVERSE REACTIONS

Adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Specialty, L.P. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Cardiac glycosides or diuretics: observe for development of cardiac arrhythmias. (7)
- Tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines: potentiate effects of epinephrine. (7)
- Beta-adrenergic blocking drugs: antagonize cardiostimulating and bronchodilating effects of epinephrine. (7)
- Alpha-adrenergic blocking drugs: antagonize vasoconstricting and hypertensive effects of epinephrine. (7)
- Ergot alkaloids: may reverse the pressor effects of epinephrine. (7)

### USE IN SPECIFIC POPULATIONS

- Elderly patients may be at greater risk of developing adverse reactions. (5.5, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling

Revised: May 2016

## FULL PRESCRIBING INFORMATION: CONTENTS\*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
  - Emergency Treatment
  - Injection-Related Complications
  - Serious Infections at the Injection Site
  - Allergic Reactions Associated with Sulfite
  - Disease Interactions
- ADVERSE REACTIONS
- DRUG INTERACTIONS
- USE IN SPECIFIC POPULATIONS
  - Pregnancy
  - Nursing Mothers

- Pediatric Use
- Geriatric Use
- OVERDOSAGE
- DESCRIPTION
- CLINICAL PHARMACOLOGY
  - Mechanism of Action
  - Pharmacodynamics
- NONCLINICAL TOXICOLOGY
  - Carcinogenesis, Mutagenesis, Impairment of Fertility
- HOW SUPPLIED/STORAGE AND HANDLING
  - How Supplied
  - Storage and Handling
- PATIENT COUNSELING INFORMATION

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

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

EpiPen and EpiPen Jr are indicated in the emergency treatment of 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 (approximately 66 pounds or more): EpiPen 0.3 mg
- Patients 15 to 30 kg (33 pounds to 66 pounds): EpiPen Jr 0.15 mg

Inject EpiPen or EpiPen Jr intramuscularly or subcutaneously 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, USP, pre-filled auto-injector
- EpiPen Jr: Injection, 0.15 mg/0.3 mL, (0.3 mL 1:2000) epinephrine injection, USP, pre-filled auto-injector

### 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) and Patient Counseling Information (17)*].

#### 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) and Patient Counseling Information (17)*].

- **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.

### 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)*].

## **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  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  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, USP) 0.3 mg and EpiPen Jr (epinephrine injection, USP) 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.

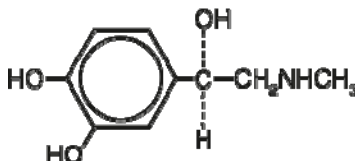
The EpiPen and EpiPen Jr each contain 2 mL epinephrine solution. Approximately 1.7 mL remains in the auto-injector after activation, but is not available for future use, and should be discarded.

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- $\alpha$ -[(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 [*see Patient Counseling Information (17)*].

## 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 subcutaneously or 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<sup>®</sup>, 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 injections, USP, 1:2000, 0.3 mL) are available as EpiPen Jr 2-Pak<sup>®</sup>, 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<sup>®</sup> and EpiPen Jr 2-Pak<sup>®</sup> also include an S-clip to clip two carrier tubes together.  
Rx only

### **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 at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. 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.

## **17 PATIENT COUNSELING INFORMATION**

[See *FDA-Approved Patient Labeling (Patient Information and Instructions for Use)*.]

A healthcare provider should review the patient instructions and operation of EpiPen and EpiPen Jr in detail, with the patient or caregiver.

Epinephrine is essential for the treatment of anaphylaxis. Patients who are at risk of or 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.

### **Administration and Training**

Instruct patients and/or caregivers in the appropriate use of EpiPen and EpiPen Jr. EpiPen should be injected into the middle of the outer thigh (through clothing, if necessary). Each device is a single-use injection. Advise patients to seek immediate medical care in conjunction with administration of EpiPen.

Instruct caregivers to hold the leg of young children firmly in place and limit movement prior to and 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 [see *Warnings and Precautions (5.2)*].

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each EpiPen or EpiPen Jr carton. A printed label on the

surface of EpiPen shows instructions for use and a diagram depicting the injection process.

Instruct patients and/or caregivers to use and practice with the Trainer to familiarize themselves with the use of EpiPen in an allergic emergency. The Trainer may be used multiple times. A Trainer device is provided in 2-Pak cartons.

### **Adverse Reactions**

Epinephrine may produce symptoms and signs that include an increase in heart rate, the sensation of a more forceful heartbeat, palpitations, sweating, nausea and vomiting, difficulty breathing, pallor, dizziness, weakness or shakiness, headache, apprehension, nervousness, or anxiety. These signs and symptoms usually subside rapidly, especially with rest, quiet and recumbency. Patients with hypertension or hyperthyroidism may develop more severe or persistent effects, and patients with coronary artery disease could experience angina. Patients with diabetes may develop increased blood glucose levels following epinephrine administration. Patients with Parkinson's disease may notice a temporary worsening of symptoms [*see Warnings and Precautions (5.5)*].

### **Accidental Injection**

Advise patients to seek immediate medical care in the case of accidental injection. Since epinephrine is a strong vasoconstrictor when injected into the digits, hands, or feet, treatment should be directed at vasodilatation if there is such an accidental injection to these areas [*see Warnings and Precautions (5.2)*].

### **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. 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 [*see Warnings and Precautions (5.3)*].

### **Storage and Handling**

Instruct patients to inspect the epinephrine solution visually through the clear window of the auto-injector periodically. Replace EpiPen and EpiPen Jr if the epinephrine solution appears discolored (pinkish or brown color), cloudy, or contains particles. Epinephrine is light sensitive and should be stored in the carrier tube provided to protect it from light. The carrier tube is not waterproof. Instruct patients that EpiPen and EpiPen Jr must be used or properly disposed once the blue safety release is removed or after use [*see Storage and Handling (16.2)*].

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

EpiPen<sup>®</sup> and EpiPen Jr<sup>®</sup> are registered trademarks of Mylan Inc. licensed exclusively to its

wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, U.S.A.

Copyright © 2016 Meridian Medical Technologies. All rights reserved.

May 2016  
MS:EPI:R2  
0001928

## **PATIENT INFORMATION and INSTRUCTIONS FOR USE**

### **EPIPEN<sup>®</sup>**

(epinephrine injection, USP) Auto-Injector 0.3 mg  
EpiPen<sup>®</sup> = one dose of 0.3 mg epinephrine (USP, 1:1000, 0.3 mL)

### **EPIPEN JR<sup>®</sup>**

(epinephrine injection, USP) Auto-Injector 0.15 mg  
EpiPen<sup>®</sup> = one dose of 0.15 mg epinephrine (USP, 1:2000, 0.3 mL)

For allergic emergencies (anaphylaxis)

### **Patient Information**

Read this Patient Information Leaflet carefully before using the EpiPen<sup>®</sup> or EpiPen Jr<sup>®</sup> Auto-Injector and each time you get a refill. There may be new information. You, your parent, caregiver, or others who may be in a position to administer EpiPen or EpiPen Jr Auto-Injector, should know how to use it before you have an allergic emergency.

This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

### **What is the most important information I should know about the EpiPen and EpiPen Jr?**

1. EpiPen and EpiPen Jr contain epinephrine, a medicine used to treat allergic emergencies (anaphylaxis). Anaphylaxis can be life threatening, can happen with minutes, and can be caused by stinging and biting insects, allergy injections, foods, medicines, exercise, or unknown causes.

Symptoms of anaphylaxis may include:

- trouble breathing
- wheezing
- hoarseness (changes in the way your voice sounds)
- hives (raised reddened rash that may itch)
- severe itching
- swelling of your face, lips, mouth, or tongue
- skin rash, redness, or swelling
- fast heartbeat
- weak pulse
- feeling very anxious
- confusion

- stomach pain
  - losing control of urine or bowel movements (incontinence)
  - diarrhea or stomach cramps
  - dizziness, fainting, or “passing out” (unconsciousness)
2. **Always carry your EpiPen or EpiPen Jr with you because you may not know when anaphylaxis may happen.**  
Talk to your healthcare provider if you need additional units to keep at work, school, or other locations. Tell your family members, caregivers, and others where you keep your EpiPen or EpiPen Jr and how to use it before you need it. You may be unable to speak in an allergic emergency.
3. **When you have an allergic emergency (anaphylaxis)**
- **Use EpiPen or EpiPen Jr right away.**
  - **Get emergency medical help right away.** You may need further medical attention. You may need to use a second EpiPen or EpiPen Jr if symptoms continue or recur. Only a healthcare provider should give additional doses of epinephrine if you need more than 2 injections for a single anaphylaxis episode.

#### **What are EpiPen and EpiPen Jr?**

- EpiPen and EpiPen Jr are disposable, prefilled automatic injection devices (auto-injectors) used to treat life-threatening, allergic emergencies including anaphylaxis in people who are at risk for or have a history of serious allergic emergencies. Each device contains a single dose of epinephrine.
- EpiPen and EpiPen Jr are for immediate self (or caregiver) administration and do not take the place of emergency medical care. You should get emergency help right away after using EpiPen and EpiPen Jr.
- EpiPen and EpiPen Jr are for people who have been prescribed this medicine by their healthcare provider.
- The EpiPen Auto-Injector (0.3 mg) is for patients who weigh 66 pounds or more (30 kilograms or more).
- The EpiPen Jr Auto-Injector (0.15 mg) is for patients who weigh about 33 to 66 pounds (15 to 30 kilograms).
- It is not known if EpiPen and EpiPen Jr are safe and effective in children who weigh less than 33 pounds (15 kilograms).

#### **What should I tell my healthcare provider before using the EpiPen or EpiPen Jr?**

**Before you use EpiPen or EpiPen Jr, tell your healthcare provider about all your medical conditions, but especially if you:**

- have heart problems or high blood pressure
- have diabetes
- have thyroid problems
- have asthma
- have a history of depression
- have Parkinson’s disease

- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if epinephrine will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if epinephrine passes into your breast milk.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Tell your healthcare provider of all known allergies.

Especially tell your healthcare provider if you take certain asthma medicines.

EpiPen or EpiPen Jr and other medicines may affect each other, causing side effects. EpiPen or EpiPen Jr may affect the way other medicines work, and other medicines may affect how EpiPen or EpiPen Jr work.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Use your EpiPen or EpiPen Jr for treatment of anaphylaxis as prescribed by your healthcare provider, regardless of your medical conditions or the medicines you take.

#### **How should I use EpiPen and EpiPen Jr?**

- Each EpiPen or EpiPen Jr Auto-Injector contains only 1 dose of medicine.
- EpiPen or EpiPen Jr should be injected into the middle of your outer thigh (upper leg). It can be injected through your clothing if needed.
- Read the Instructions for Use at the end of this Patient Information Leaflet about the right way to use EpiPen and EpiPen Jr.
- Your healthcare provider will show you how to safely use the EpiPen or EpiPen Jr Auto-Injector.
- Use your EpiPen or EpiPen Jr exactly as your healthcare provider tells you to use it. You may need to use a second EpiPen or EpiPen Jr if symptoms continue or recur. Only a healthcare provider should give additional doses of epinephrine if you need more than 2 injections for a single anaphylaxis episode.
- **Caution: Never put your thumb, fingers, or hand over the orange tip. Never press or push the orange tip with your thumb, fingers, or hand.** The needle comes out of the orange tip. Accidental injection into finger, hands or feet may cause a loss of blood flow to these areas. **If this happens, go immediately to the nearest emergency room.** Tell the healthcare provider where on your body you received the accidental injection.
- Your EpiPen and EpiPen Jr Auto-Injector may come packaged with an EpiPen Trainer and separate Trainer Instructions for Use. **The EpiPen Trainer has a grey color. The grey EpiPen Trainer contains no medicine and no needle.** Periodically practice with your EpiPen Trainer before an allergic emergency happens to make sure you are able to safely use the real EpiPen and EpiPen Jr Auto-Injector in an emergency. Always carry your real EpiPen or

EpiPen Jr Auto-Injector with you in case of an allergic emergency. Additional training resources are available at [www.epipen.com](http://www.epipen.com).

- Do not drop the carrier tube or auto-injector. If the carrier tube or auto-injector is dropped, check for damage and leakage. Dispose of the auto-injector and carrier tube, and replace if damage or leakage is noticed or suspected.

### **What are the possible side effects of the EpiPen and EpiPen Jr?**

**EpiPen and EpiPen Jr may cause serious side effects.**

- **The EpiPen or EpiPen Jr should only be injected into the middle of your outer thigh (upper leg). Do not** inject the EpiPen or EpiPen Jr into your:
  - veins
  - buttocks
  - fingers, toes, hands, or feet

If you accidentally inject EpiPen or EpiPen Jr into any other part of your body, go to the nearest emergency room right away. Tell the healthcare provider where on your body you received the accidental injection.

- Rarely, patients who have used EpiPen or EpiPen Jr may develop infections at the injection site within a few days of an injection. Some of these infections can be serious. Call your healthcare provider right away if you have any of the following at an injection site:
  - redness that does not go away
  - swelling
  - tenderness
  - the area feels warm to the touch
- Cuts on the skin, bent needles, and needles that remain in the skin after the injection, have happened in young children who do not cooperate and kick or move during an injection. If you inject a young child with EpiPen or EpiPen Jr, hold their leg firmly in place before and during the injection to prevent injuries. Ask your healthcare provider to show you how to properly hold the leg of a young child during injection.
- **If you have certain medical conditions, or take certain medicines, your condition may get worse or you may have longer lasting side effects when you use your EpiPen or EpiPen Jr.** Talk to your healthcare provider about all your medical conditions.

Common side effects of EpiPen and EpiPen Jr include:

- fast, irregular or “pounding” heartbeat
- sweating
- headache
- weakness
- shakiness

- paleness
- feelings of over excitement, nervousness or anxiety
- dizziness
- nausea or vomiting
- breathing problems

These side effects may go away with rest. **Tell your healthcare provider if you have any side effect that bothers you or that does not go away.**

These are not all the possible side effects of the EpiPen or EpiPen Jr. For more information, ask your healthcare provider or pharmacist.

**Call your healthcare provider for medical advice about side effects.** You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store EpiPen and EpiPen Jr?**

- Store EpiPen and EpiPen Jr at room temperature between 68° to 77° F (20° to 25° C).
- Protect from light.
- **Do not** expose to extreme cold or heat. For example, **do not** store in your vehicle's glove box and **do not** store in the refrigerator or freezer.
- Examine the contents in the clear window of your auto-injector periodically. The solution should be clear. If the solution is discolored (pinkish or brown color) or contains solid particles, replace the unit.
- Always keep your EpiPen or EpiPen Jr Auto-Injector in the carrier tube to protect it from damage; however, the carrier tube is not waterproof.
- The blue safety release helps to prevent accidental injection. Keep the blue safety release on until you need to use EpiPen or EpiPen Jr.
- Your EpiPen or EpiPen Jr has an expiration date. Replace it before the expiration date.

**Keep EpiPen and EpiPen Jr and all medicines out of the reach of children.**

#### **General information about the safe and effective use of EpiPen and EpiPen Jr**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use the EpiPen or EpiPen Jr for a condition for which it was not prescribed. Do not give your EpiPen or EpiPen Jr to other people.

This Patient Information Leaflet summarizes the most important information about EpiPen and EpiPen Jr. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about EpiPen and EpiPen Jr that is written for health professionals.

For more information and video instructions on the use of EpiPen and EpiPen Jr, go to [www.epipen.com](http://www.epipen.com) or call 1-800-395-3376.

#### **What are the ingredients in EpiPen and EpiPen Jr?**



**Active Ingredients:** Epinephrine

**Inactive Ingredients:** sodium chloride, sodium metabisulfite, hydrochloric acid, and water.

#### **Important Information**

- The EpiPen Auto-Injector has a yellow colored label.
- The EpiPen Jr Auto-Injector has a green colored label.
- The EpiPen Trainer has a grey color and contains no medicine and no needle.
- Your auto-injector is designed to work through clothing.
- The blue safety release on the EpiPen and EpiPen Jr Auto-Injector helps to prevent accidental injection of the device. Do not remove the blue safety release until you are ready to use it.
- Only inject into the middle of the outer thigh (upper leg). Never inject into any other part of the body.
- Never put your thumb, fingers, or your hand over the orange tip. The needle comes out of the orange tip.
- If an accidental injection happens, get medical help right away.
- Do not place patient information or any other foreign objects in the carrier tube with the Auto-Injector, as this may prevent you from removing the Auto-Injector for use.

## Instructions for Use

### EPIPEN<sup>®</sup>

(epinephrine injection, USP) Auto-Injector 0.3 mg  
EpiPen<sup>®</sup> = one dose of 0.3 mg epinephrine (USP, 1:1000, 0.3 mL)

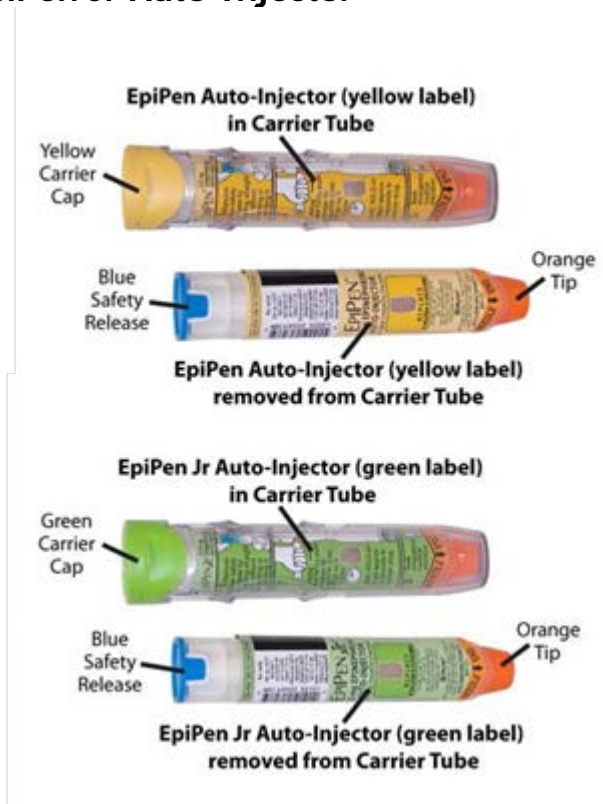
### EPIPEN JR<sup>®</sup>

(epinephrine injection, USP) Auto-Injector 0.15 mg  
EpiPen<sup>®</sup> = one dose of 0.15 mg epinephrine (USP, 1:2000, 0.3 mL)

For allergic emergencies (anaphylaxis)

Read these Instructions for Use carefully before you use EpiPen or EpiPen Jr. Before you need to use your EpiPen or EpiPen Jr, make sure your healthcare provider shows you the right way to use it. Parents, caregivers, and others who may be in a position to administer EpiPen or EpiPen Jr Auto-Injector should also understand how to use it as well. If you have any questions, ask your healthcare provider.

### Your EpiPen and EpiPen Jr Auto-Injector



A dose of EpiPen or EpiPen Jr requires 3 simple steps: Prepare, Administer

and Get emergency medical help

### Step 1. Prepare EpiPen or EpiPen Jr for injection

**Remove the EpiPen or EpiPen Jr from the clear carrier tube.**



Flip open the yellow cap of your EpiPen or the green cap of your EpiPen Jr carrier tube.



Tip and slide the auto-injector out of the carrier tube.



**Grasp the auto-injector in your fist with the orange tip (needle end) pointing downward.**

With your other hand, **remove the blue safety release by pulling straight up** without bending or twisting it.

#### **Note:**

- The needle comes out of the orange tip.
- To avoid an accidental injection, never put your thumb, fingers or hand over the orange tip. If an accidental injection happens, get medical help right away

### Step 2. Administer EpiPen or EpiPen Jr

**If you are administering EpiPen or EpiPen Jr to a young child, hold the leg firmly in place while administering an injection.**



Place the orange tip against the middle of the outer thigh (upper leg) at a right angle (perpendicular) to the thigh.

**Swing and push the auto-injector firmly** until it 'clicks'. The

click signals that the injection has started.



**Hold firmly in place for 3 seconds (count slowly 1,2,3).**  
The injection is now complete.



**Remove the auto-injector from the thigh.** The orange tip will extend to cover the needle. If the needle is still visible, do not attempt to reuse it.



Massage the injection area for 10 seconds.

### **Step 3. Get emergency medical help now.**

You may need further medical attention. **You may need to use a second EpiPen or EpiPen Jr Auto-Injector if symptoms continue or recur.**

- Take your used auto-injector with you when you go to see a healthcare provider.
- Tell the healthcare provider that you have received an injection of epinephrine. Show the healthcare provider where you received the injection.
- Give your used EpiPen or EpiPen Jr Auto-Injector to the healthcare provider for inspection and proper disposal.
- Ask for a refill, if needed.

#### **Note:**

- The used auto-injector with extended needle cover will not fit in the carrier tube.
- EpiPen and EpiPen Jr are single-use injectable devices that deliver a fixed dose of epinephrine. The auto-injector cannot be reused. Do not attempt to reuse EpiPen after the device has been activated. It is normal for most of the medicine to remain in the auto-injector after the dose is injected. The correct dose has been administered if the orange needle tip is extended and the window is blocked.
- Your EpiPen and EpiPen Jr Auto-Injector may come packaged with an EpiPen Trainer and separate Trainer Instructions for Use. The EpiPen Trainer has a grey color. The grey EpiPen Trainer contains no medicine and no needle. Practice with your EpiPen Trainer, but always carry your real EpiPen or EpiPen

- Jr Auto-Injector in case of an allergic emergency.
- If you will be administering EpiPen or EpiPen Jr to a young child, ask your healthcare provider to show you how to properly hold the leg in place while administering a dose.
- Do not try to take the EpiPen or EpiPen Jr Auto-Injector apart.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

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

EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of, Morgantown, WV 26505, U.S.A.

Copyright © 2016 Meridian Medical Technologies. All rights reserved.

Revised: May 2016

MS: PIL: EPI: R2

0001927

**EPIPEN®**

(epinephrine injection, USP) Auto-Injector 0.3 mg

EpiPen® = one dose of 0.3 mg epinephrine (USP, 1:1000, 0.3 mL)

**EPIPEN JR®**

(epinephrine injection, USP) Auto-Injector 0.15 mg

EpiPen® = one dose of 0.15 mg epinephrine (USP, 1:2000, 0.3 mL)

**MyEpiPen.com**

Register your EpiPen or EpiPen Jr Auto-Injector at **MyEpiPen.com** and find out more about:

- Free EpiPen Auto-Injector **Refill Reminder Program**. It is important to keep your auto-injector up-to-date.

Register up to 6 EpiPen or EpiPen Jr Auto- Injectors and receive automatic **Refill Reminder Alerts**.

- Receive periodic information related to allergies and allergens.
- Instructional Video

For more information about EpiPen or EpiPen Jr Auto-Injectors and proper use of the product, call Mylan at 1-877-446-3679 or visit [www.epipen.com](http://www.epipen.com).



## EpiPen® Trainer Instructions for Use

### EpiPen Trainer Instructions for Use

**In an emergency: Do not use the grey Trainer. Use your real yellow EpiPen® or green EpiPen Jr® Auto-Injector.**

#### Important Information

- **The Trainer label has a grey color.**
- **The Trainer contains no medicine and no needle.**
- Periodically practice with the grey colored Trainer before an allergic emergency (anaphylaxis) happens to make sure you are able to safely use the real yellow EpiPen or green EpiPen Jr Auto-Injector in case of an emergency.
- Always carry your real yellow EpiPen or green EpiPen Jr Auto-Injector in case of an allergic emergency.

### The EpiPen Trainer

Familiarize yourself with this grey Trainer. Practice until you are comfortable using it.

**Your grey colored Trainer:**



- Never put your thumb, other fingers, or hand over the Orange Tip.
- The Orange Tip is where the needle comes out of your EpiPen or EpiPen Jr Auto-Injector.

## Practice Instructions



### 1 Prepare the Trainer for Simulated Injection

- **Grasp the grey Trainer in your fist with the orange tip pointing downward.**
- With your other hand, **remove blue safety release by pulling straight up** without bending or twisting it.
- Removing the blue safety release unlocks the Trainer.

### 2 Administer the Trainer Simulation

- **If practicing with a young child, hold the leg firmly in place while using the EpiPen Trainer.** Ask your healthcare provider to show you how to properly hold the leg to practice so that you will be prepared before an allergic emergency happens.



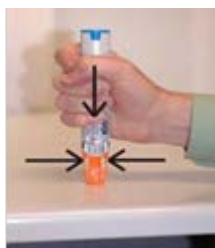
- Place the orange tip against the middle of the outer thigh (upper leg) at a right angle (perpendicular) to the thigh.
- **Swing and push the trainer firmly** until it 'clicks.' The click signals that the injection has started.

- **Hold firmly in place for 3 seconds (count slowly 1,2,3).**
- **Remove the Trainer from the thigh** and massage the injection area for 10 seconds. The orange tip automatically extends out after use.



#### Note:

- In an actual emergency, you would need to seek medical help right away
- The actual auto-injector is made to work through clothing
- Do not inject into any other part of the body



### 3 To reset the Trainer

- Put the blue safety release back on the Trainer
- Place the orange tip on a hard surface
- Squeeze the sides of the orange tip and push down on the Trainer with the other hand

**Note: With the real yellow EpiPen or green EpiPen Jr Auto-Injector, the orange tip covers the needle after self-injection to help protect you from accidentally sticking yourself or others.**



## Practice Session Information

**In case of an allergic emergency, use the real yellow EpiPen or green EpiPen Jr Auto-Injector and not the grey Trainer.**

Follow instructions above. Repeat as often as needed until you are able to self-inject quickly and correctly.

Reread:

- These Trainer Instructions for Use
- The “Patient Information” that comes with your EpiPen or EpiPen Jr Auto-Injector

Train others who could help you in an emergency:

- Your parents, caregivers, and others who may be in a position to administer EpiPen or EpiPen Jr should know how to help you during an allergic emergency (anaphylaxis). Before an emergency occurs, have them:
  - Practice activating the Trainer
  - Read these Trainer Instructions and the “Patient Information”

For more information about the EpiPen and EpiPen Jr Auto-Injector and the proper use of the products, go to [www.epipen.com](http://www.epipen.com).

### Caution:

**Important differences between the Trainer and your real yellow EpiPen or green EpiPen Jr Auto-Injector**



	TRAINER (Grey)	EpiPen (Yellow)	EpiPen Jr (Green)
Contains medication?	NO	YES	YES
Has needle?	NO	YES	YES
Comes in Carrier Tube?	NO	YES	YES
Color of Label	Grey	Yellow	Green
Has expiration date?	NO	YES	YES
Can be reused?	YES	NO (use only once)	NO (use only once)
Okay to remove and replace safety release?	YES	NO (remove just once before use)	NO (remove just once before use)
Pressure needed to hold against thigh?	Moderate	Strong	Strong

This Trainer Instructions for Use has been approved by the U.S. Food and Drug Administration.

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

EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, U.S.A.

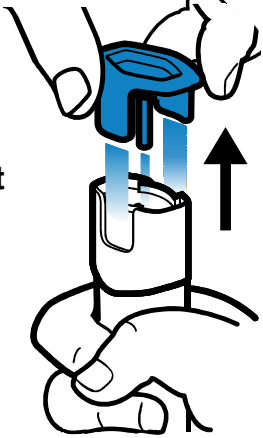
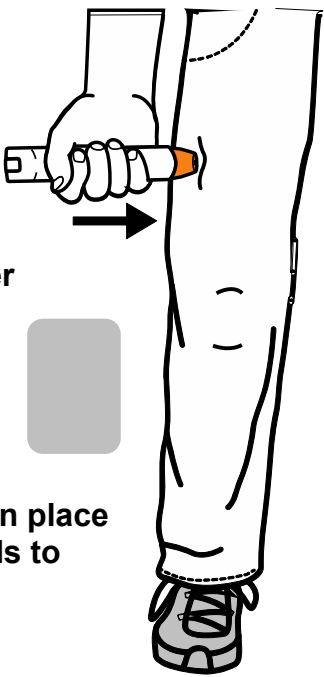


Copyright © 2016 Meridian Medical Technologies. All rights reserved.

Revised: May 2016

MS:EPIT:R2

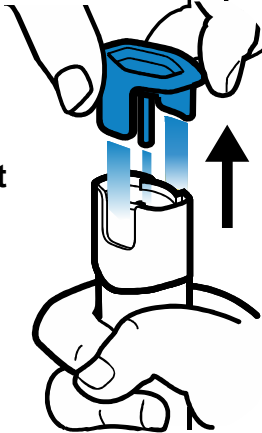
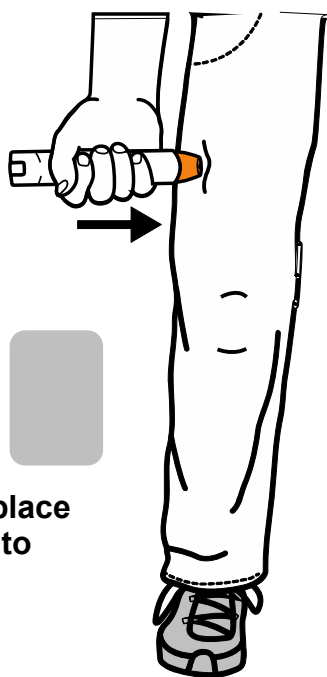


0001929

0.3 mg – Label

<b>EpiPen<sup>®</sup></b> (epinephrine injection, USP) Auto-Injector 0.3 mg	EpiPen <sup>®</sup> Auto-Injector utilizes Truject <sup>®</sup> technology. US Patent 7,449,012 • 0001930 • MS:50001:LB:R3		See other side for instructions	
<p><b>1</b> Remove blue safety release by pulling straight up without bending or twisting it.</p> 			<p><b>Rx only</b></p> <p>After use, most of liquid stays in auto-injector and can't be reused. Delivers 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL). Each 0.3 mL also contains 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite.</p>	
<p><b>2</b> Swing and push firmly the orange tip against outer thigh so it "clicks"</p> <p><b>:03</b></p> <p>Hold firmly in place for 3 seconds to deliver drug</p> 	EpiPen <sup>®</sup> is a registered trademark of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA		<p><b>EpiPen<sup>®</sup></b> (epinephrine injection, USP) <b>Auto-Injector 0.3 mg</b> for Allergic Emergencies (Anaphylaxis)</p> <div data-bbox="873 1014 1382 1318">  <p><b>REPLACE</b> IF SOLUTION IS DISCOLORED</p> </div> <p><b>STORE AT 68° TO 77° F (20° TO 25°C)</b> <b>DO NOT REFRIGERATE</b> <b>PROTECT FROM LIGHT</b></p> <p> <b>Mylan<sup>®</sup></b></p> <p>Mfd. for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc. Columbia, MD 21046, USA, a Pfizer company</p> <p>Copyright © 2016 Meridian Medical Technologies. All rights reserved.</p>	
<p><b>3 GET EMERGENCY MEDICAL HELP!</b></p>			<p><b>Made in U.S.A.</b></p>	
<p><b>NEEDLE ↓ END</b></p>			<p><b>NEEDLE ↓ END</b></p>	

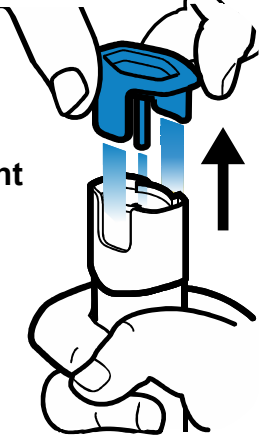
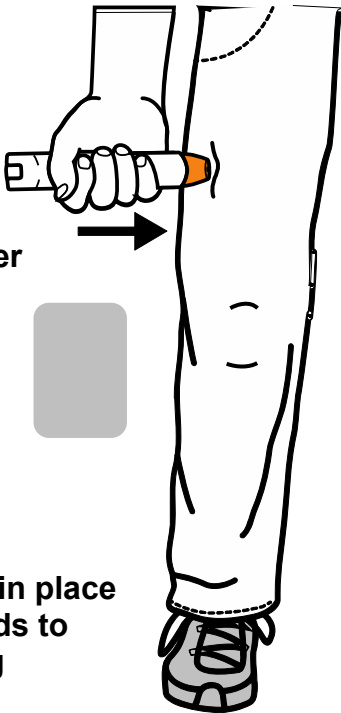




0.3 mg – Label Professional Sample

<b>EpiPen<sup>®</sup></b> (epinephrine injection, USP) Auto-Injector 0.3 mg		See other side for instructions	
<b>1</b> Remove blue safety release by pulling straight up without bending or twisting it		<b>EpiPen<sup>®</sup></b> Auto-Injector utilizes Truject <sup>®</sup> technology. US Patent 7,449,012 • 0001937 • MS:50099:LB:R3	<b>Rx only</b> After use, most of liquid stays in auto-injector and can't be reused. Delivers 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL). Each 0.3 mL also contains 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite.
<b>2</b> Swing and push firmly the orange tip against outer thigh so it "clicks" <b>:03</b> Hold firmly in place for 3 seconds to deliver drug			<b>Professional Sample – Not For Sale</b> <b>EpiPen<sup>®</sup></b> (epinephrine injection, USP) <b>Auto-Injector 0.3 mg</b> for Allergic Emergencies (Anaphylaxis)  <b>REPLACE</b> <b>IF SOLUTION IS DISCOLORED</b> <b>STORE AT 68° TO 77° F</b> <b>(20° TO 25°C)</b> <b>DO NOT REFRIGERATE</b> <b>PROTECT FROM LIGHT</b>  Mfd. for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc. Columbia, MD 21046, USA, a Pfizer company Copyright © 2016 Meridian Medical Technologies. All rights reserved. <b>Made in U.S.A.</b>
<b>3</b> GET EMERGENCY MEDICAL HELP!		<b>EpiPen<sup>®</sup></b> is a registered trademark of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA	
NEEDLE ↓ END			NEEDLE ↓ END



0.15 mg – Label

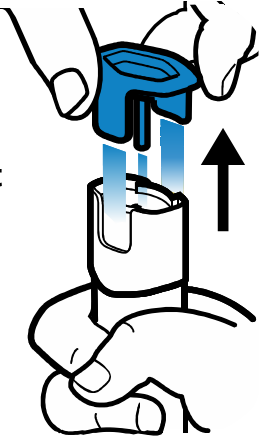
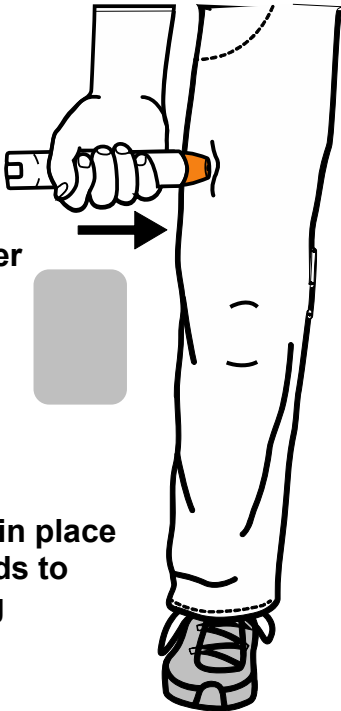


<b>EpiPen Jr<sup>®</sup></b> (epinephrine injection, USP) Auto-Injector 0.15 mg		See other side for instructions	
<b>1</b> Remove blue safety release by pulling straight up without bending or twisting it 		<b>Rx only</b> After use, most of liquid stays in auto-injector and can't be reused. Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection 1:2000 USP (0.3 mL). Each 0.3 mL also contains 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite.	
<b>2</b> Swing and push firmly the orange tip against outer thigh so it "clicks"  :03 Hold firmly in place for 3 seconds to deliver drug		<b>EpiPen Jr<sup>®</sup></b> (epinephrine injection, USP) <b>Auto-Injector 0.15 mg</b> for Allergic Emergencies (Anaphylaxis)  <b>REPLACE</b> <b>IF SOLUTION IS DISCOLORED</b> <b>STORE AT 68° TO 77° F</b> <b>(20° TO 25°C)</b> <b>DO NOT REFRIGERATE</b> <b>PROTECT FROM LIGHT</b>  Mfd. for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc. Columbia, MD 21046, USA, a Pfizer company Copyright © 2016 Meridian Medical Technologies. All rights reserved.	
<b>3 GET EMERGENCY MEDICAL HELP!</b>		<b>Made in U.S.A.</b>	
NEEDLE ↓ END		NEEDLE ↓ END	

EpiPen Jr<sup>®</sup> Auto-Injector utilizes Truject<sup>®</sup> technology.  
US Patent 7,449,012 • 0001931 • MS:50101:LB:R3

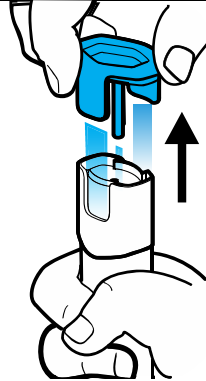
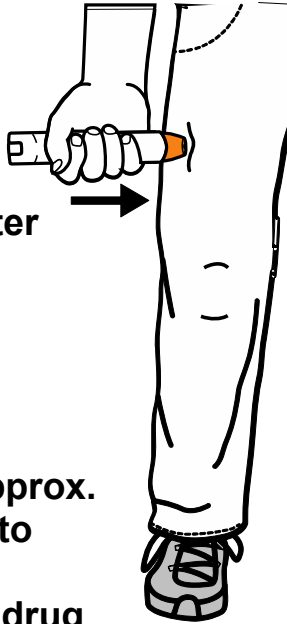
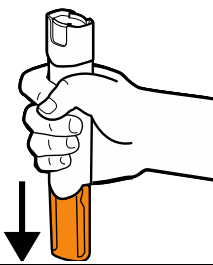
EpiPen Jr<sup>®</sup> is a registered trademark of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P., of Morgantown, WV 26505, USA



0.15 mg– Label Professional Sample

<b>EpiPen Jr<sup>®</sup></b> (epinephrine injection, USP) Auto-Injector 0.15 mg		See other side for instructions	
<b>1</b> Remove blue safety release by pulling straight up without bending or twisting it 	<b>EpiPen Jr<sup>®</sup></b> Auto-Injector utilizes Truject <sup>®</sup> technology. US Patent 7,449,012 • 0001938• MS:50199:LB:R3	<b>(3) NDC49502 50199 (9)</b>	<b>Rx only</b> After use, most of liquid stays in auto-injector and can't be reused. Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection 1:2000 USP (0.3 mL). Each 0.3 mL also contains 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite.
<b>2</b> Swing and push firmly the orange tip against outer thigh so it "clicks"  <b>:03</b> Hold firmly in place for 3 seconds to deliver drug	<b>EpiPen Jr<sup>®</sup></b> is a registered trademark of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P., of Morgantown, WV 26505, USA	<b>Professional Sample – Not For Sale</b>  <b>EpiPen Jr<sup>®</sup></b> (epinephrine injection, USP) <b>Auto-Injector 0.15 mg</b> for Allergic Emergencies (Anaphylaxis)   <b>REPLACE</b> <b>IF SOLUTION IS DISCOLORED</b>  <b>STORE AT 68° TO 77° F</b> <b>(20° TO 25°C)</b> <b>DO NOT REFRIGERATE</b> <b>PROTECT FROM LIGHT</b>	
<b>3 GET EMERGENCY MEDICAL HELP!</b>		 Mfd. for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc. Columbia, MD 21046, USA, a Pfizer company Copyright © 2016 Meridian Medical Technologies. All rights reserved. <b>Made in U.S.A.</b>	
<b>NEEDLE ↓ END</b>		<b>NEEDLE ↓ END</b>	

## Trainer – Label (front)

<b>NO MEDICINE NO NEEDLE</b>	
<b>TRAINER</b> FOR PRACTICE ONLY	
<b>1</b> Remove blue safety release by pulling straight up without bending or twisting it	
<b>2</b> Swing and push firmly the orange tip against outer thigh so it “clicks” <b>:03</b> <b>AND HOLD</b> on thigh approx. 3 seconds to simulate delivery of drug	
<b>3</b> Tip extends after use	
MS:50000:LBF:R3	0001932

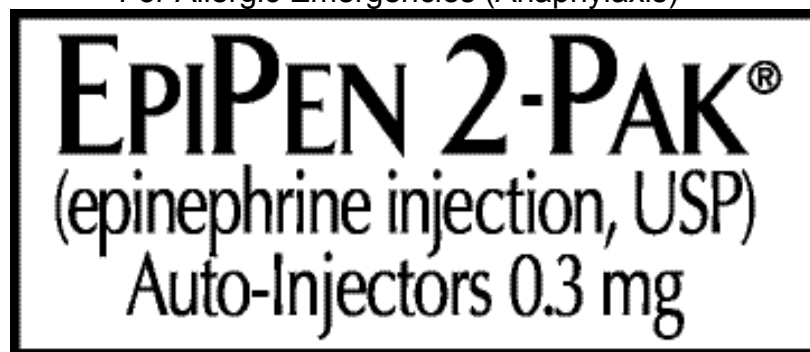


**0.3 mg - CARTON - Principal Display Panel**

NDC 49502-500-02

*Rx only*

For Allergic Emergencies (Anaphylaxis)



Each carton contains:

**Two yellow EpiPen®  
Auto-Injectors**



**One grey Trainer**



Register your EpiPen® Auto-Injectors at [www.epipen.com](http://www.epipen.com)  
to receive free refill reminders







### 0.3 mg - CARTON - Left Panel

MS:50002:2C:R2 0001935	<div><b>EPIPEN 2-PAK<sup>®</sup></b> (epinephrine injection, USP) Auto-Injectors 0.3 mg</div> <p>Never put thumb, fingers or hand over orange tip. Do <b>not</b> remove blue safety release until ready to use.</p> <p><b>EpiPen 2-Pak<sup>®</sup></b> contains 2 <b>EpiPen<sup>®</sup></b> Auto-Injectors and 1 Trainer. Each <b>EpiPen<sup>®</sup></b> Auto-Injector delivers one 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL). Discard unit after use. The Trainer contains no medicine and no needle. Read enclosed patient package insert carefully before using.</p>
---------------------------	---

### 0.3 mg - CARTON - Right Panel

<div><b>EPIPEN 2-PAK<sup>®</sup></b> (epinephrine injection, USP) Auto-Injectors 0.3 mg</div>	<p><b>Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.</b></p> <p>Manufactured for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company EpiPen<sup>®</sup> and EpiPen Jr<sup>®</sup> are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA Copyright © 2016 Meridian Medical Technologies. All rights reserved.</p> <p><b>(3) 49502 50002 (2)</b></p>
---	--

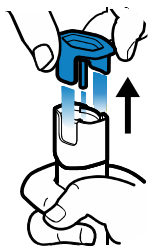


0.3 mg - CARTON - Back Panel

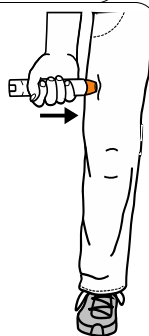
Open this End

See enclosed Patient Information Leaflet for complete instructions for use.

- 1** Remove the blue safety release by pulling straight up without bending or twisting it



- 2** Swing and push firmly the orange tip against outer thigh so it "clicks"



**:03**

Hold firmly in place for 3 seconds to deliver drug

- 3** GET EMERGENCY MEDICAL HELP!

**Note:** The needle comes out of the orange tip.  
Never put your thumb, fingers or hand over the orange tip.

Code

Scan here to learn more



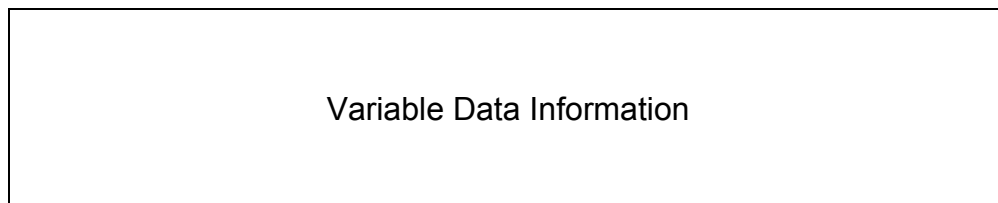
**EPIPEN 2-PAK<sup>®</sup>**  
(epinephrine injection, USP)  
Auto-Injectors 0.3 mg



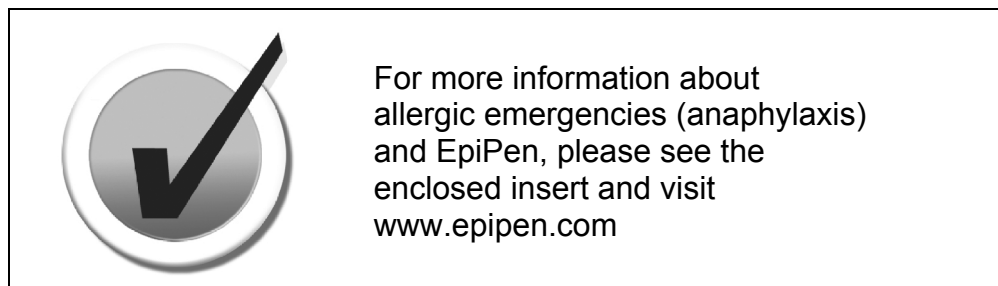
**0.3 mg - CARTON – Top Flap**



**0.3 mg - CARTON – Bottom Flap**



**0.3 mg - CARTON – Inside Top and Bottom Flaps**





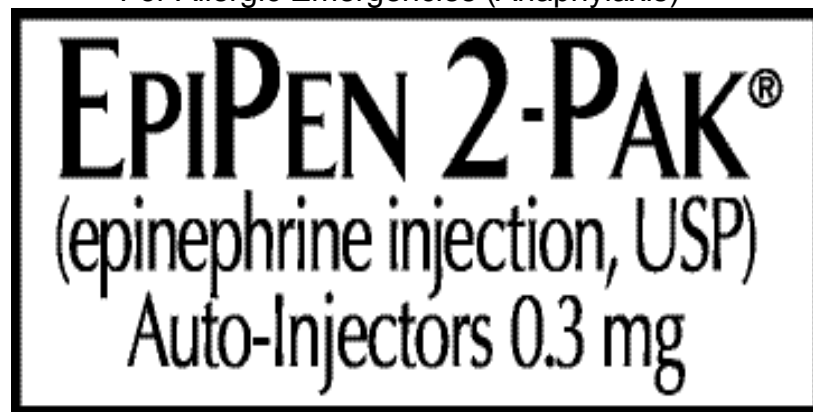
0.3 mg – CARTON - Professional Sample - Principal Display Panel

**Professional Sample – Not For Sale**

NDC 49502-500-92

For Allergic Emergencies (Anaphylaxis)

*Rx only*



Each carton contains:

**Two yellow EpiPen®**  
Auto-Injectors



**One grey Trainer**

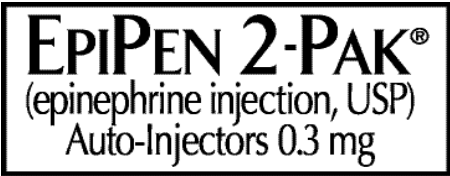


Register your EpiPen® Auto-Injectors at [www.epipen.com](http://www.epipen.com)  
to receive free refill reminders

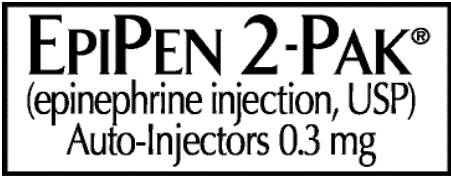




### 0.3 mg – CARTON - Professional Sample - Left Panel

<div>MS:50092:2C:R2</div> <div>0001939</div>	<div><b>Professional Sample – Not For Sale</b></div> <div></div> <div>Never put thumb, fingers or hand over orange tip. Do <b>not</b> remove blue safety release until ready to use.</div> <div>EpiPen 2-Pak® contains 2 EpiPen® Auto-Injectors and 1 Trainer. Each EpiPen® Auto-Injector delivers one 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL). Discard unit after use. The Trainer contains no medicine and no needle. Read enclosed patient package insert carefully before using.</div>
--	---

### 0.3 mg – CARTON - Professional Sample - Right Panel

	<div></div> <div>Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.</div> <div>Manufactured for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA Copyright © 2016 Meridian Medical Technologies. All rights reserved.</div> <div><b>(3) 49502 50092 (3)</b></div>
--	---

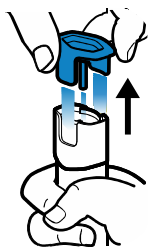


**0.3 mg – CARTON - Professional Sample - Back Panel**

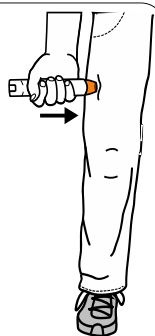
Open this End

See enclosed Patient Information Leaflet for complete instructions for use.

- 1** Remove the blue safety release by pulling straight up without bending or twisting it



- 2** Swing and push firmly the orange tip against outer thigh so it "clicks"



**:03**

Hold firmly in place for 3 seconds to deliver drug

- 3** GET EMERGENCY MEDICAL HELP!

**Note:** The needle comes out of the orange tip.  
Never put your thumb, fingers or hand over the orange tip.

Code

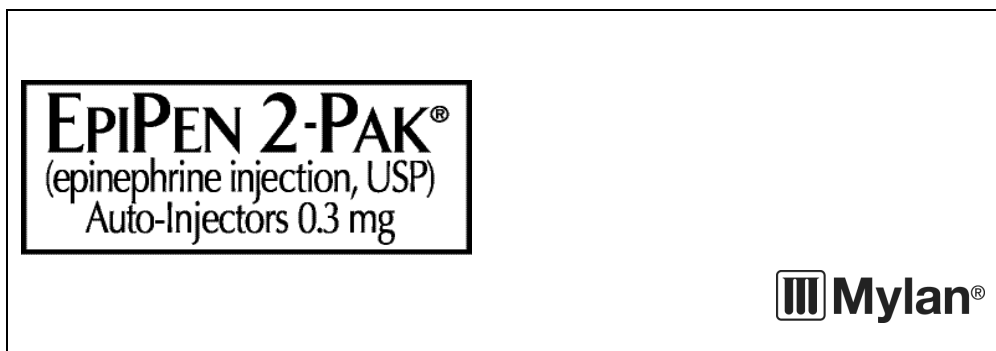
Scan here to learn more



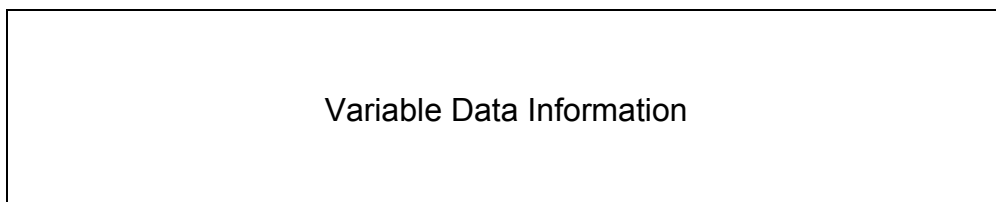
**EPIPEN 2-PAK<sup>®</sup>**  
(epinephrine injection, USP)  
Auto-Injectors 0.3 mg



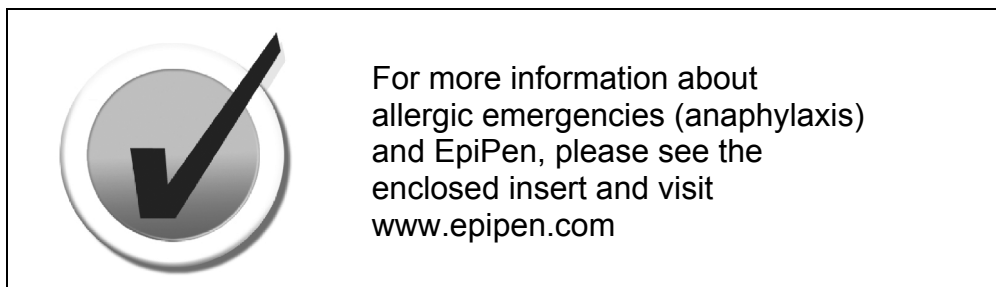
**0.3 mg – CARTON - Professional Sample – Top Flap**



**0.3 mg – CARTON - Professional Sample – Bottom Flap**



**0.3 mg – CARTON - Professional Sample - Inside Top and Bottom Flaps**



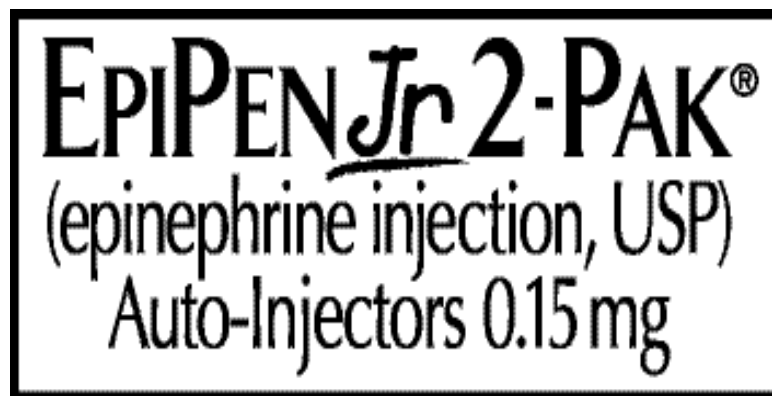


0.15 mg - CARTON - Principal Display Panel

NDC 49502-501-02

For Allergic Emergencies (Anaphylaxis)

*Rx only*



Each carton contains:

**Two green EpiPen Jr®  
Auto-Injectors**



**One grey Trainer**



Register your EpiPen Jr® Auto-Injectors at [www.epipen.com](http://www.epipen.com)  
to receive free refill reminders





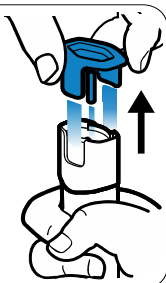


## 0.15 mg - CARTON - Back Panel

Open this End

See enclosed Patient Information Leaflet for complete instructions for use.

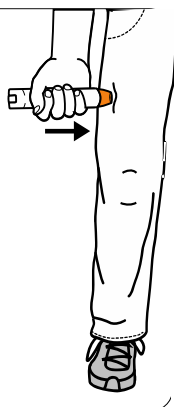
- 1 Remove the blue safety release by pulling straight up without bending or twisting it



- 2 Swing and push firmly the orange tip against outer thigh so it "clicks"

:03

Hold firmly in place for 3 seconds to deliver drug



- 3 GET EMERGENCY MEDICAL HELP!

**Note:** The needle comes out of the orange tip.  
Never put your thumb, fingers or hand over the orange tip.

Code

Scan here to learn more



**EpiPEN Jr 2-PAK<sup>®</sup>**  
(epinephrine injection, USP)  
Auto-Injectors 0.15 mg



**0.15 mg - CARTON - Right Panel**

0001936 MS:50102:2C:R2	<div><b>EPIPEN<sub>Jr</sub> 2-PAK<sup>®</sup></b> (epinephrine injection, USP) Auto-Injectors 0.15 mg</div> <p><b>Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.</b></p> <p>Manufactured for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company EpiPen<sup>®</sup> and EpiPen Jr<sup>®</sup> are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA Copyright © 2016 Meridian Medical Technologies. All rights reserved.</p> <p><b>(3) 49502 50102 (9)</b></p>
---------------------------	--

**0.15 mg - CARTON - Left Panel**

<div><b>EPIPEN<sub>Jr</sub> 2-PAK<sup>®</sup></b> (epinephrine injection, USP) Auto-Injectors 0.15 mg</div>	<p>Never put thumb, fingers or hand over orange tip. Do <b>not</b> remove blue safety release until ready to use.</p> <p><b>EpiPen Jr 2-Pak<sup>®</sup></b> contains 2 <b>EpiPen Jr<sup>®</sup></b> Auto-Injectors and 1 Trainer. Each <b>EpiPen Jr<sup>®</sup></b> Auto-Injector delivers one 0.15 mg intramuscular dose of epinephrine from epinephrine injection 1:2000 USP (0.3 mL). Discard unit after use. The Trainer contains no medicine and no needle. Read enclosed patient package insert carefully before using.</p>
---	---



**0.15 mg - CARTON – Top Flap**

**EpiPEN<sub>Jr</sub> 2-PAK<sup>®</sup>**  
(epinephrine injection, USP)  
Auto-Injectors 0.15 mg



**0.15 mg - CARTON – Bottom Flap**

Variable Data Information

**0.15 mg - CARTON - Inside Top and Bottom Flaps**



For more information about  
allergic emergencies (anaphylaxis)  
and EpiPen, please see the  
enclosed insert and visit  
[www.epipen.com](http://www.epipen.com)



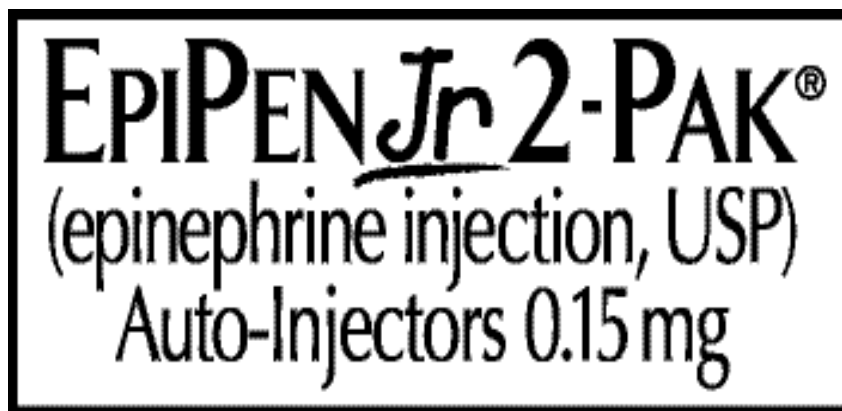
0.15 mg – CARTON - Professional Sample - Principal Display Panel

**Professional Sample – Not For Sale**

NDC 49502-501-92

For Allergic Emergencies (Anaphylaxis)

*Rx only*



Each carton contains:

**Two green EpiPen Jr®**  
Auto-Injectors

**One grey Trainer**



Register your EpiPen Jr® Auto-Injectors at [www.epipen.com](http://www.epipen.com)  
to receive free refill reminders





## 0.15 mg – CARTON - Professional Sample - Left Panel

MS:50192:2C:R2 0001940	<p><b>Professional Sample – Not For Sale</b></p> <p><b>EPIPEN<sub>Jr</sub> 2-PAK<sup>®</sup></b> (epinephrine injection, USP) Auto-Injectors 0.15 mg</p>	<p>Never put thumb, fingers or hand over orange tip. Do <b>not</b> remove blue safety release until ready to use.</p> <p><b>EpiPen Jr<sup>®</sup> 2-Pak<sup>®</sup></b> contains 2 <b>EpiPen Jr<sup>®</sup></b> Auto-Injectors and 1 Trainer. Each <b>EpiPen Jr<sup>®</sup></b> Auto-Injector delivers one 0.15 mg intramuscular dose of epinephrine from epinephrine injection 1:2000 USP (0.3 mL). Discard unit after use. The Trainer contains no medicine and no needle. Read enclosed patient package insert carefully before using.</p>
---------------------------	--	---

## 0.15 mg – CARTON - Professional Sample - Right Panel

<p><b>EPIPEN<sub>Jr</sub> 2-PAK<sup>®</sup></b> (epinephrine injection, USP) Auto-Injectors 0.15 mg</p>	<p><b>Replace if discolored. Store at 68° to 77°F</b> <b>(20° to 25°C). Do not refrigerate.</b> <b>Protect from light.</b></p> <p>Manufactured for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company EpiPen<sup>®</sup> and EpiPen Jr<sup>®</sup> are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA Copyright © 2016 Meridian Medical Technologies. All rights reserved.</p>	<p><b>(3) 49502 50192 (0)</b></p>
---	--	-----------------------------------

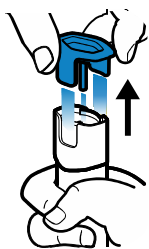


## 0.15 mg – CARTON - Professional Sample - Back Panel

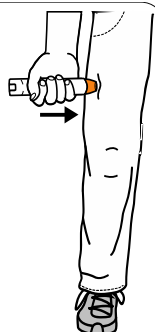
Open this End

See enclosed Patient Information  
Leaflet for complete instructions for use.

- 1** Remove the  
blue safety  
release by  
pulling straight  
up without  
bending or  
twisting it



- 2** Swing and push  
firmly the orange tip  
against outer  
thigh so it  
“clicks”



**:03**

Hold firmly in place  
for 3 seconds  
to deliver drug

- 3** GET EMERGENCY MEDICAL HELP!

**Note:** The needle comes out of the orange tip.  
Never put your thumb, fingers or hand over the orange tip.

Code

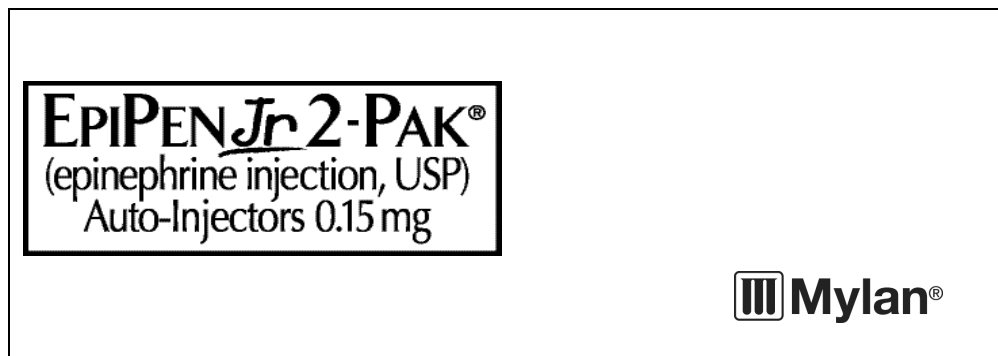
Scan here to  
learn more



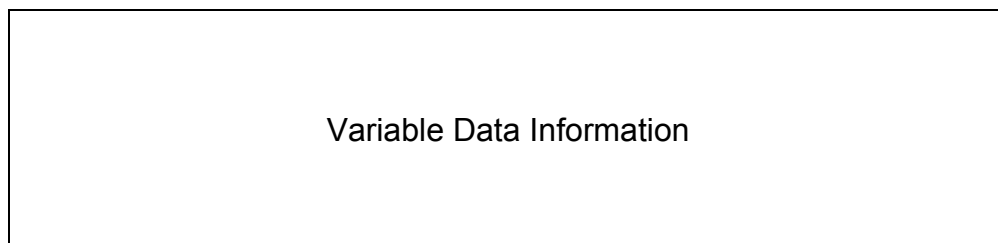
**EpiPEN Jr 2-PAK®**  
(epinephrine injection, USP)  
Auto-Injectors 0.15 mg



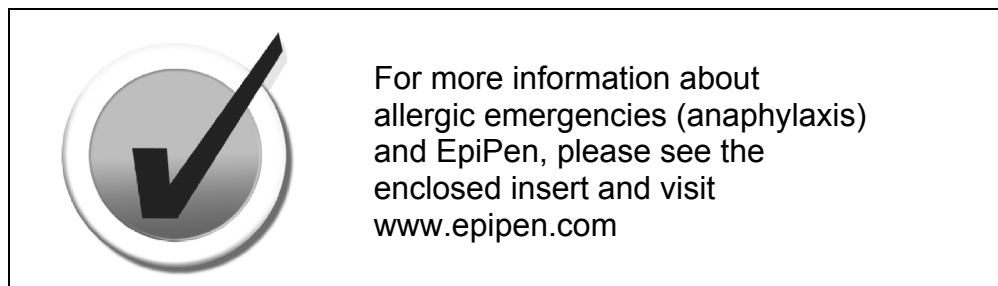
**0.15 mg – CARTON - Professional Sample – Top Flap**



**0.15 mg – CARTON - Professional Sample – Bottom Flap**



**0.15 mg – CARTON - Professional Sample - Inside Top and Bottom Flaps**



-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SALLY M SEYMOUR  
05/18/2016



**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019430Orig1s061**

**MEDICAL REVIEW(S)**

## MEDICAL OFFICER REVIEW

### Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

<b>APPLICATION:</b>	NDA# 19430, S-061	<b>TRADE NAME:</b>	EpiPen®, EpiPen Jr® Auto-Injector
<b>APPLICANT/SPONSOR:</b>	Mylan Specialty LP	<b>USAN NAME:</b>	Epinephrine injection, USP
<b>MEDICAL OFFICER:</b>	Peter Starke, MD	<b>CATEGORY:</b>	Catecholamine: nonselective alpha and beta adrenergic agonist
<b>DEPUTY DIRECTOR FOR SAFETY:</b>	Sally Seymour, MD		
<b>DATE:</b>	May 2, 2016	<b>ROUTE:</b>	Intramuscular or subcutaneous

#### SUBMISSIONS REVIEWED IN THIS DOCUMENT / OTHER RELEVANT DOCUMENTS

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
October 30, 2015			Information request regarding lacerations after use of EpiPen
November 20, 2015		SD-1208	Response to IR of October 30, 2015
February 5, 2016			FDAAA Safety Labeling Change (SLC) notification letter
March 4, 2016	March 4, 2016	SD-1258	New supplement in response to February 5, 2016 FDAAA SLC
March 24, 2016			Labeling IR#1
April 7, 2016	April 7, 2016	SD-1269	Response to Labeling IR of March 4, 2016
April 15, 2016			Labeling IR #2
April 20, 2016	April 20, 2016	SD-1277	Response to Labeling IR of April 15, 2016

#### REVIEW SUMMARY:

This is a review of a labeling supplement submitted by Mylan to NDA 19430 for EpiPen® (epinephrine injection, USP) Auto-Injector 0.3 mg, and EpiPen Jr® (epinephrine injection, USP) Auto-Injector 0.15 mg. The supplement was submitted in response to a February 5, 2016, FDAA, Safety Labeling Changes Notification Letter for two safety issues of lacerations and embedded needles caused by epinephrine auto-injector use in children, and Clostridial infections following injection of epinephrine for treatment of anaphylaxis. These safety issues were each the subject of a Tracked Safety Issue (TSI) involving each of the approved epinephrine products, TSI 1541 for lacerations, etc., and TSI 1555 for Clostridial infections.

After labeling negotiations, the agreed upon labeling is recommended for approval.

#### OUTSTANDING ISSUES:

None.

#### RECOMMENDED REGULATORY ACTION

**NDA/SUPPLEMENTS:**  X  **APPROVAL**   **COMPLETE RESPONSE**  
**OTHER ACTION:**

## I. Introduction

This is a review of a labeling supplement (S-061) submitted by Mylan to NDA 19430 for EpiPen® (epinephrine injection, USP) Auto-Injector 0.3 mg, and EpiPen Jr® (epinephrine injection, USP) Auto-Injector 0.15 mg. The supplement was submitted in response to two safety issues of lacerations and embedded needles caused by epinephrine auto-injector use in children, and Clostridial infections following injection of epinephrine for treatment of anaphylaxis. These safety issues were each the subject of a Tracked Safety Issue (TSI) involving each of the approved epinephrine products, TSI 1541 for lacerations, etc., and TSI 1555 for Clostridial infections.

## II. Lacerations, bent needles, and embedded needles

This safety issue (TSI 1541) is based upon a publication summarizing reports of lacerations and embedded needles after epinephrine injection from epinephrine auto-injectors for treatment of anaphylaxis [Brown JC, Tuuri RE, Akhter S, et al. Lacerations and Embedded Needles Caused by Epinephrine Autoinjector Use in Children. *Annals of Emergency Medicine* 2016;67:307-15.e8]. The authors assessed emergency medicine email discussion lists and social media allergy groups to identify epinephrine autoinjector injuries involving children. They identified 22 cases, including 17 children with lacerations and 5 other needle-related traumas associated with epinephrine auto-injector use (all EpiPen devices) in children. Some of the lacerations required sutures to close the wounds, and some left scars.

Information requests were sent to the three application holders the approved epinephrine auto-injector products on October 30, 2015, informing the sponsors of the information regarding lacerations and requesting a response regarding how each company proposed to deal with the safety issue. The Division also requested information on injection time. The following is a brief summary of the responses from Mylan.

- Mylan reviewed its available safety data and identified 59 cases of lacerations. The review noted that a third of cases were associated with the patient moving, pulling away, jerking, kicking, etc., during administration. Mylan also identified 25 cases associated with bent needle, some of which were associated with movement during administration and some with potentially use in children below the recommended weight in product labeling. Overall, given the number of products sold in the US (> (b) (4) units), the number of reports suggests that these events are rare.
- Mylan indicated that based upon functional release testing data, the mean injection (dispense) time for EpiPen is 0.17 (SD = 0.03) seconds, and the maximum dispense time is 0.30 (SD = 0.33) seconds. The response included references to a technical report previously submitted by the previous NDA holder, Meridian Medical Technologies, to the Agency with data supporting the injection time [Meridian Medical Technologies, Technical Report MTR 12-013, submitted to NDA 19430, S-053 on June 4, 2012], as well as references to publications containing independently conducted dispense-time testing of EpiPen Auto-Injectors. The current labeled injection hold time is 10 seconds.
- In response to this safety issue, Mylan suggested the following the following actions:
  - Add labeling to instruct the user to restrain the child prior to injection

- Reduce injection time hold to 3 seconds.
- Remove language indicating the injection is complete following 10 second hold time
- Clarify that the autoinjector should not be re-used
- Use of other forms of injectable epinephrine if appropriate.

Responses from all three companies were analyzed and the Division determined that labeling recommendations to immobilize a child's leg during administration may limit the lacerations with epinephrine injection. Additionally, the Division considered that the data submitted and/or referenced by Mylan support Mylan's request for a shorter injection hold time, and that this shortened time might reduce the likelihood of lacerations while parents or caregivers are trying to maintain the needle in the thigh of a child who is fighting an injection.

On February 5, 2016, the Division requested FDAAA Safety Labeling Changes (SLC) to add information to the DOSAGE AND ADMINISTRATION section to immobilize a child's leg prior to and during epinephrine injection. Given that there are two additional epinephrine solution products that are approved for anaphylaxis and Epinephrine Injection, 1 mg/mL (1:1000), these products were also included in the FDAAA safety labeling change requests.

### III. Clostridial infections

The safety issue of Clostridial infections at the site of injection post-epinephrine treatment (TSI 1555) was based upon the report of a case of Clostridial infection of the thigh of a teenage patient after injection of epinephrine via an epinephrine auto-injector (EpiPen) at home for the treatment of an anaphylactic reaction. FDA initiated a review to determine if there was a product quality (e.g. contamination) issue with EpiPen. The investigation was coordinated by the Division of Counter Terrorism and Emergency Coordination Staff. The investigation included: obtaining the used EpiPen and the 2<sup>nd</sup> unopened EpiPen for microbiological testing; information requests to Mylan; coordinating microbiological testing at the FDA Denver Laboratory; and inspection of Mylan manufacturing facility. Results of the full investigation revealed no contamination issues.

A review of FAERS and the literature was also conducted to identify whether the safety issue extended beyond the one case report. The review identified sporadic case reports of *Clostridium perfringens* infection associated with epinephrine injection dating back to the 1960s. There were 5 FAERS reports and multiple literature reports. The risk of Clostridial infection is not a new safety issue with epinephrine injection for anaphylaxis. *Clostridium* can be a skin contaminant. Given that epinephrine injection for anaphylaxis is an emergency situation, the skin is not prepped prior to administration and regardless, alcohol prep would not kill *Clostridium* spores. Since epinephrine causes local vasoconstriction, the anaerobic environment could foster a Clostridial infection. Thus, scattered reports of *Clostridium* infection following epinephrine injection for anaphylaxis is not surprising. Many of the older cases were associated with injection into the buttocks; therefore all of the products include a Warning to not inject into the buttocks to minimize the risk of gas gangrene.

However, information about the rare risk of serious localized infection in the thigh following epinephrine administration is not currently in the epinephrine labels. In addition, a delay in

diagnosis of gas gangrene was noted in some cases. Therefore, raising awareness about the risk of Clostridial infection was deemed appropriate as well as statements informing patients to seek care if signs or symptoms of infection develop.

Requests for FDAAA Safety Labeling Changes to add a new WARNING along with additional information in the HIGHLIGHTS, ADVERSE REACTIONS and PATIENT COUNSELING INFORMATION sections were sent to the application holders for all of the approved epinephrine products on February 5, 2016. In addition to the application holders of the three epinephrine auto-injectors listed above, a request was also sent to the application holder of Adrenalin and Epinephrine Injection, 1 mg/mL (1:1000), as both of these products are indicated for anaphylaxis.

#### IV. Labeling

The agreed class labeling (Warnings and Precautions) for the above safety issues is summarized below. Note that the Division decided that only the auto-injectors need to have the safety issue of injection related injuries added as a Warning and Precaution. The epinephrine injection products that are administered in a hospital/clinic setting only have additional class language regarding the need to hold the leg during the injection in the Dosage and Administration section. In addition to changes to the Warnings and Precautions, related changes were incorporated in the Dosage and Administration, Adverse Reactions, Patient Information, and Instructions for Use (IFU) sections. Specifically, the new Instructions for Use include the class statement that “If you are administering [product name] to a young child, hold the leg firmly in place (b) (4) while administering an injection.” The agreed upon language is very similar to the original language in the February 9, 2016, FDAAA SLC Notification Letter.

#### ***New Warnings and Precautions***

The following class labeling is being added to Section 5.2, Injection-Related Complications:

**Hold the leg firmly during injection.** Lacerations, bent needles, and embedded needles have been reported when [product name] has 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 [product name] to young children, instruct caregivers to hold the child’s leg firmly in place and limit movement prior to and during injection.

The following class labeling is being added as a new section:

**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 [product name] into the buttock. 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.

### ***Other Labeling Changes***

As noted above, all factors that contribute to the safe use of these products were considered as part of these supplements. In that regard, each manufacturer was asked to respond to specific safety questions regarding their product as well as to provide safety suggestions as to how to address these issues. As part of their response, Mylan proposed to change the Instructions for Use to a 3-second hold time after triggering the injection, and they provided and/or referenced the data to support this request. After review, the Division found that Mylan's request is reasonable, in light of the fact that 1) this shortened time might reduce the likelihood of lacerations while parents or caregivers are trying to maintain the needle in the thigh of a child who is fighting an injection, and 2) the shortened hold time still factors in a large safety margin over the actual injection time. As a result, the instruction set in the EpiPen IFU (and in other locations of the EpiPen labeling) was changed from the current "Hold firmly against the thigh for approximately 10 seconds to deliver the drug" to an instruction to "Hold firmly in place for 3 seconds (count slowly 1, 2, 3)" before removing the auto-injector from the thigh.

## **V. Recommendations**

The clinical recommendation is approval of this labeling supplement.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

PETER R STARKE  
05/02/2016

SALLY M SEYMOUR  
05/02/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019430Orig1s061**

**CHEMISTRY REVIEW(S)**



CHEMIST'S REVIEW <i>Review #1</i>		1. ORGANIZATION Branch 1/DPMA 1/OLDP/OPQ	2. NDA NUMBER 019430
3. NAME AND ADDRESS OF APPLICANT ( <i>City and State</i> ) Mylan Specialty L.P. P.O. Box 4310 781 Chestnut Ridge Road Morgantown, WV 26504-4310  <u>Applicant's Responsible Official:</u> S. Wayne Talton, Head Global Regulatory Science and Operations, Mylan, Inc. Tel: (304) 599-2595, Ext 6551 Fax: (304) 285-6407 e-mail: wayne.talton@mylan.com		4. AF NUMBER	
		5. SUPPLEMENT (S) NUMBER(S) DATES(S) <b>S-061; PAS; SDN 1258</b> Letter Date: 03/04/2016 Received Date:03/04/2016 <b>S-061[BL]; SDN 1269*</b> Letter Date: 04/07/2016 Received Date:04/07/2016 <b>S-061[BL]; SDN 1277*</b> Letter Date: 04/07/2016 Received Date:04/07/2016 <b>Due Date: 07/04/2016</b> <b>* No formal assignment made!</b> <b>Subject of current review.</b>	
6. NAME OF DRUG EpiPen Auto-Injector	7. NONPROPRIETARY NAME Epinephrine Injection		
8. SUPPLEMENT PROVIDES FOR: Labeling Revisions in Accordance with the Agency's Correspondence Dated March 24, 2016.			
9. PHARMACOLOGICAL CATEGORY Indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis.	10. HOW DISPENSED RX <u>  </u> OTC <u>  </u>	11. RELATED IND/NDA/DMF	
12. DOSAGE FORM(S) sterile injectable solution	13. POTENCY 0.3 mg/0.3 mL and 0.15 mg/0.3 mL		
14. CHEMICAL NAME AND STRUCTURE (-)-3,4- Dihydroxy- $\alpha$ -[(methylamino)methyl]benzyl alcohol See USAN Dictionary		15. RECORDS AND REPORTS CURRENT YES__NO__ REVIEWED YES__NO__	
16. COMMENTS: <i>Section 11 ( DESCRIPTION ) and section 16 (HOW SUPPLIED/STORAGE AND HANDLING) were reviewed. There are no changes.</i>  <u>Changes in Instructions for Use consistent with revised Package Insert and Patient Instructions for Use.</u> These changes have been reviewed by the clinical team and found to be acceptable. The injection hold time has been modified from 10 seconds to 3 seconds. The clinical team has reviewed this information and agreed to this modification.			
17. CONCLUSIONS AND RECOMMENDATIONS The labeling changes are acceptable from CMC standpoint.			
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE On file	DATE COMPLETED May 13, 2016	

**Background:**

Reference is made to the New Drug Application (NDA) identified above and to our prior approval supplement submitted on March 4, 2016 (S-061) which provided safety labeling changes under 505(o)(4). Reference is also made to the Agency's March 24, 2016 correspondence with recommendations and comments regarding the labeling for the proposed prescribing information, patient information and instructions for use, and trainer instructions for use. Reference is also made to the Agency's March 31, 2016 correspondence which granted us with an extension until April 8, 2016 to provide revised labeling.

In accordance with the Agency's request, Mylan is submitting revised draft prescribing information (insert code MS:EPI:R2; Revised March 2016, patient information and instructions for use code MS:PIL:EPI:R2; Revised March 2016 and trainer instructions for use code MS:EPIT:R2; Revised March 2016) and corresponding draft carton and container labels. Please refer to Sections 1.14.1.3 and 1.14.1.1, respectively. Although the Agency did not provide any comments on the container and carton labeling, please note that enclosed container and carton labeling have been revised from those previously submitted for editorial changes. Labeling revisions are denoted using tracked changes and corresponding clean MS Word documents are provided for your reference and ease of review.

Draft Structured Product Labeling (SPL) that has been revised consistent with the proposed draft prescribing information is provided in Section 1.14.1.3. The tracked changes and corresponding clean MS Word documents are provided.

**Review:**

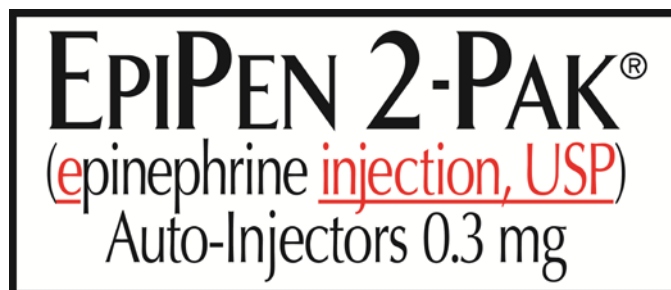
Pertinent sections of the draft labeling are reviewed.

**Evaluation:    Acceptable**

*Section 11 ( DESCRIPTION ) and section 16 (HOW SUPPLIED/STORAGE AND HANDLING) were Reviewed. There are no changes.*

**Carton and Container labeling were modified as follows:**

- Add USP and injection in established name
- Changes in Instructions for Use consistent with revised Package Insert and Patient Instructions for Use. These changes have been reviewed by the clinical team and found to be acceptable. The injection hold time has been modified from 10 seconds to 3 seconds. The clinical team has reviewed this information and agreed to this modification.



**CONCLUSION AND RECOMMENDATION:**

The labeling changes are acceptable from CMC standpoint.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CHONG HO KIM  
05/13/2016

RAMESH RAGHAVACHARI  
05/13/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019430Orig1s061**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

---

---

**FACSIMILE TRANSMITTAL SHEET**

---

---

**DATE:** April 15, 2016

<b>To:</b> S. Wayne Talton Head, Global Regulatory Science And Operation	<b>From:</b> Carol Hill, M.S. Safety Regulatory Project Manager
<b>Company:</b> Mylan Specialty, L.P.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>E-address:</b> <a href="mailto:wayne.talton@mylan.com">wayne.talton@mylan.com</a>	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 304-599-2594, ext. 6551	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 19430/S-061- FDA Labeling Revision II

**Total no. of pages including  
cover:** 29

**Comments:**

---

---

<b>Document to be mailed:</b>	<b>YES</b>	<b>xNO</b>
-------------------------------	------------	------------

---

---

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 19430/S-061  
Mylan Specialty LP  
EpiPen

Dear Mr. Talton:

Please refer to your supplement dated March 4, 2016, and the amendment to this supplement dated April 7, 2016. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert (PI), Patient Information Leaflet (PIL), Instructions for Use (IFU), and Trainer Information for Use (TIFU). The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these labeling revisions are not necessarily our final recommendations and that additional changes may be forthcoming.

If applicable, we request that you update the carton and container labeling to reflect any of the PI and IFU labeling changes.

Submit draft labeling in tracked-changes and clean word versions by COB on April 22, 2016. If you have any questions, please contact Carol F. Hill, Safety Regulatory Project Manager, at 301-796-1226.

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CAROL F HILL  
04/15/2016





**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

---

---

**FACSIMILE TRANSMITTAL SHEET**

---

---

**DATE:** March 31, 2016

<b>To:</b> S. Wayne Talton Head, Global Regulatory Science and Operation	<b>From:</b> Carol Hill, M.S. Safety Regulatory Project Manager
<b>Company:</b> Mylan Specialty, L.P.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>E-address:</b> <a href="mailto:wayne.talton@mylan.com">wayne.talton@mylan.com</a>	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 304-599-2594, ext. 6551	<b>Phone number:</b> 301-796-2300

**Subject:** Extension of Time to Submit Response to Labeling Revisions Fax

**Total no. of pages including cover:** 3

**Comments:**

---

---

<b>Document to be mailed:</b>	<b>YES</b>	<b><input checked="" type="checkbox"/> NO</b>
-------------------------------	------------	---

---

---

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.**

NDA 19430/S-061  
Mylan Specialty LP  
EpiPen

Dear Mr. Talton:

We refer to the safety labeling changes, requested on March 24, 2016, with requested response by April 4, 2008. It has been requested that we allow for additional time for you to review our revised labeling and submit the requested response. We have re-considered the timeline for the request and will allow additional time to respond.

We are now requesting that you submit your response no later than close of business on April 8, 2016. If you have any questions, please contact Carol F. Hill, Safety Regulatory Project Manager, at 301-796-1226.

Drafted by: CHill/3-31-16  
Clearance: SSeymour/3-31-16  
Finalized: CHill/3-31-16

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CAROL F HILL  
03/31/2016



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

---

---

**FACSIMILE TRANSMITTAL SHEET**

---

---

**DATE:** March 24, 2016

<b>To:</b> S.Wayne Talton Head, Global Regulatory Science and Operation	<b>From:</b> Carol Hill, M.S. Safety Regulatory Project Manager
<b>Company:</b> Mylan Specialty, L.P.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>E-address:</b> <a href="mailto:wayne.talton@mylan.com">wayne.talton@mylan.com</a>	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 304-599-2594, ext. 6551	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 19430/S-061 – FDA Labeling Revisions

**Total no. of pages including  
cover:** 25

**Comments:**

---

---

<b>Document to be mailed:</b>	YES	xNO
-------------------------------	-----	-----

---

---

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 19430/S-061  
Mylan Specialty, L.P.  
EpiPen

Dear Mr. Talton:

Your labeling submission dated March 4, 2016, is currently under review. We are providing our recommendations and comments in the attached labeling for the proposed Package Insert (PI), Patient Information Leaflet (PIL), Instructions for Use (IFU), and Trainer Instructions for Use (TIFU). The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these labeling revisions are not necessarily our final recommendations and that additional changes may be forth coming.

We did not specifically address the carton and container labeling submitted. However, our recommendations and comments regarding changes to the other labeling would apply, i.e., changes to the IFU would apply to any instructions on the carton and container labels as well.

We request that you submit draft labeling to incorporate these revisions by April 4, 2016. If you have any questions, please contact Carol F. Hill, Safety Regulatory Project Manager, at 301-796-1226.

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CAROL F HILL  
03/24/2016



NDA 19430/S-061

**LABELING DISCUSSION EXTENSION**

Mylan Specialty L. P.  
791 Chestnut Ridge Road  
P. O. Box 4310  
Morgantown, WV 26504-4310

Attention: S. Wayne Talton  
Head, Global Regulatory Science and Operations

Dear Mr. Talton:

Please refer to your March 4, 2016, supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EpiPen and EpiPen Jr. (epinephrine injection) Auto-Injector, 0.3 mg and 0.15 mg.

On February 5, 2016, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of EpiPen to address the risk of lacerations and embedded needles after injection and serious infection (e.g. *Clostridium perfringens*) at the injection site, with the use of epinephrine, based on new safety information about these risks identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On March 4, 2016, we received your prior approval supplement containing your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplement and, if we disagree with the proposed changes, to initiate discussions with you. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that a 30-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for this supplement ends on May 3, 2016.

If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager for Safety, at (301) 796-1226.



Sincerely,

*{See appended electronic signature page}*

Sally Seymour, MD  
Deputy Director for Safety  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SALLY M SEYMOUR  
03/23/2016