

# EPINEPHRINE- epinephrine injection

## Lineage Therapeutics Inc

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### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPINEPHRINE INJECTION, USP AUTO-INJECTOR safely and effectively. See full prescribing information for EPINEPHRINE INJECTION, USP AUTO-INJECTOR.

**Epinephrine injection, USP auto-injector 0.3 mg, 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

Epinephrine injection, USP auto-injector contains 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): Epinephrine injection, USP auto-injector 0.3 mg (2)
- Patients 15 to 30 kg (33 lbs-66 lbs): Epinephrine injection, USP auto-injector 0.15 mg (2)

Inject epinephrine injection, USP auto-injector 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

- Injection, 0.3 mg: 0.3 mg/0.3 mL epinephrine injection, USP, pre-filled auto-injector (3)
- Injection, 0.15 mg: 0.15 mg/0.15 mL epinephrine injection, 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 Lineage Therapeutics Inc. at 1-888-894-6528 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: 5/2016

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

Epinephrine injection, USP auto-injector is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which includes bees, wasps, hornets, yellow jackets and fire ants), and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media), and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

Epinephrine injection, USP auto-injector is intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.

Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension,

syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria, or angioedema.

Epinephrine injection, USP auto-injector is intended for immediate administration as emergency supportive therapy only and is not a replacement or substitute for immediate medical care.

## 2 DOSAGE AND ADMINISTRATION

Selection of the appropriate epinephrine injection, USP auto-injector dosage strength is determined according to patient body weight.

- Patients greater than or equal to 30 kg (approximately 66 pounds or more): epinephrine injection, USP auto-injector 0.3 mg
- Patients 15 to 30 kg (33 pounds to 66 pounds): epinephrine injection, USP auto-injector 0.15 mg

Inject epinephrine injection, USP auto-injector intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Instruct caregivers of young children who are prescribed an epinephrine injection, USP auto-injector 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 epinephrine injection, USP auto-injector contains a single dose of epinephrine for single use injection. Since the doses of epinephrine delivered from epinephrine injection, USP auto-injector are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are deemed necessary.

The prescriber should carefully assess each patient to determine the most appropriate dose of epinephrine, recognizing the life-threatening nature of the reactions for which this drug is indicated.

With severe persistent anaphylaxis, repeat injections with an additional epinephrine injection, USP auto-injector 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 viewing window of epinephrine injection, USP auto-injector should be inspected visually for particulate matter and discoloration. Epinephrine is light sensitive and should be stored in the outer case provided to protect it from light [see *How Supplied/Storage and Handling (16.2)*].

## 3 DOSAGE FORMS AND STRENGTHS

- Injection, 0.3 mg/0.3 mL epinephrine injection, USP, pre-filled auto-injector
- Injection, 0.15 mg/0.15 mL epinephrine injection, USP, pre-filled auto-injector

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Emergency Treatment

Epinephrine injection, USP auto-injector is intended for immediate administration as emergency supportive therapy and is 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

Epinephrine injection, USP auto-injector 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 a 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 the development of Clostridial infections (gas gangrene). Cleansing with alcohol does not kill bacterial spores, and therefore, does not lower the 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 epinephrine 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 epinephrine injection, USP auto-injector 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 epinephrine injection, USP auto-injector 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 bisulfite, 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 epinephrine injection, USP auto-injector 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 epinephrine injection, USP auto-injector has been injected into the thigh of young children who are uncooperative and kick or move during an injection [see *Warnings 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 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 epinephrine injection, USP auto-injector is administered to a nursing woman.

### **8.4 Pediatric Use**

Epinephrine injection, USP auto-injector 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 dose of epinephrine delivered from epinephrine injection, USP auto-injector is 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, epinephrine injection, USP auto-injector 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) and 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 a 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

Epinephrine injection, USP auto-injector 0.3 mg and 0.15 mg is an auto-injector and a combination product containing drug and device components.

Each epinephrine injection, USP auto-injector 0.3 mg delivers a single dose of 0.3 mg epinephrine from epinephrine injection, USP (0.3 mL) in a sterile solution.

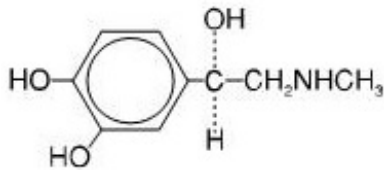
Each epinephrine injection, USP auto-injector 0.15 mg delivers a single dose of 0.15 mg epinephrine from epinephrine injection, USP (0.15 mL) in a sterile solution.

Epinephrine injection, USP auto-injector 0.3 mg and epinephrine injection, USP auto-injector 0.15 mg each contain 1.1 mL of epinephrine solution. 0.3 mL and 0.15 mL epinephrine solution are dispensed for epinephrine injection, USP auto-injector 0.3 mg and epinephrine injection, USP auto-injector 0.15 mg, respectively, when activated. The solution remaining after activation is not available for future use and should be discarded.

Each 0.3 mL in epinephrine injection, USP auto-injector 0.3 mg contains 0.3 mg epinephrine, 2.6 mg sodium chloride, not more than 1.5 mg chlorobutanol, 0.45 mg sodium bisulfite, hydrochloric acid and sodium hydroxide to adjust pH, and water for injection. The pH range is 2.2-5.0.

Each 0.15 mL in epinephrine injection, USP auto-injector 0.15 mg contains 0.15 mg epinephrine, 1.3 mg sodium chloride, not more than 0.75 mg chlorobutanol, 0.225 mg sodium bisulfite, hydrochloric acid and sodium hydroxide 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 epinephrine injection, USP auto-injector if the epinephrine solution appears discolored (pinkish or brown color), cloudy, or contains particles.

Thoroughly review the patient instructions and operation of epinephrine injection, USP auto-injector 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 intramuscularly or subcutaneously, 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

Carton containing two epinephrine injection, USP auto-injectors 0.3 mg: NDC 54505-102-02.



Carton containing one epinephrine injection, USP auto-injector 0.3 mg: NDC 54505-102-01.

Carton containing two epinephrine injection, USP auto-injectors 0.15 mg: NDC 54505-101-02.

Carton containing one epinephrine injection, USP auto-injector 0.15 mg: NDC 54505-101-01.

Rx only

## **16.2 Storage and Handling**

Protect from light. Epinephrine is light sensitive and should be stored in the carrying-case provided to protect it from light. Store at room temperature (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 epinephrine injection, USP auto-injector, in detail, with the patient or caregiver.

Epinephrine is essential for the treatment of anaphylaxis. Carefully instruct 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, about the circumstances under which epinephrine should be used.

### **Administration and Training**

Instruct patients and/or caregivers in the appropriate use of epinephrine injection, USP auto-injector. Epinephrine injection, USP auto-injector should be injected into the middle of the outer thigh (through clothing if necessary).

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 epinephrine injection, USP auto-injector has been injected into the thigh of young children who are uncooperative and kick during an injection [see *Warnings and Precautions (5.2)*].

Each epinephrine injection, USP auto-injector is a single-use injection. Advise patients to seek immediate medical care in conjunction with administration of epinephrine injection, USP auto-injector.

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each epinephrine injection, USP auto-injector carton. A printed label on the surface of epinephrine injection, USP auto-injector shows instructions for use and a diagram depicting the injection process.

Instruct patients and/or caregivers to use the Trainer to familiarize themselves with the use of epinephrine injection, USP auto-injector in an allergic emergency. The Trainer may be used multiple times.

### **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 vasodilation 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 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 viewing window periodically. Replace epinephrine injection, USP auto-injector if the epinephrine solution appears discolored (pinkish or brown), cloudy, or contains particles. Epinephrine is light sensitive, store in the outer case provided to protect it from light. Instruct patients that epinephrine injection, USP auto-injector must be properly disposed of once the blue caps have been removed or after use [see *How Supplied/Storage and Handling (16.2)*].

Complete patient information, including dosage, directions for proper administration and precautions are provided inside each epinephrine injection, USP auto-injector carton.

Manufactured for and Distributed by: Lineage Therapeutics Inc., Horsham, PA 19044

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For inquiries call 1-888-894-6528

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## **Patient Information**

EPINEPHRINE INJECTION, USP AUTO-INJECTOR (ep-in-eph-rine)

Authorized generic of Adrenaclick®

For allergic emergencies (anaphylaxis)

Read this Patient Information Leaflet carefully before you use the epinephrine injection, USP 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 epinephrine injection, USP 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 epinephrine injection, USP auto-injector?**

1. Epinephrine injection, USP auto-injector contains epinephrine, a medicine used to treat allergic emergencies (anaphylaxis). Anaphylaxis can be life-threatening, can happen within minutes, and can be caused by stinging and biting insects, allergy injections, foods, medicines, exercise, or other unknown causes. Symptoms of an 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 epinephrine injection, USP auto-injector 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 epinephrine injection, USP auto-injector 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 epinephrine injection, USP auto-injector right away.**
- **Get emergency medical help right away.** You may need further medical attention. You may need to use a second epinephrine injection, USP auto-injector 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 is epinephrine injection, USP auto-injector?**

- Epinephrine injection, USP auto-injector is a disposable, prefilled automatic injection device (auto-injector) 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.
- Epinephrine injection, USP auto-injector is for immediate self (or caregiver) administration and does not take the place of emergency medical care. You should get emergency medical help right away after using epinephrine injection, USP auto-injector.
- Epinephrine injection, USP auto-injector is for people who have been prescribed this medicine by their healthcare provider.
- The epinephrine injection, USP auto-injector 0.3 mg auto-injector is for patients who weigh 66 pounds or more (30 kilograms or more).
- The epinephrine injection, USP auto-injector 0.15 mg auto-injector is for patients who weigh about 33 to 66 pounds (15 to 30 kilograms).
- It is not known if epinephrine injection, USP auto-injector is safe and effective in children who weigh less than 33 pounds (15 kilograms).

**What should I tell my healthcare provider before using epinephrine injection, USP auto-injector?**

**Before you use epinephrine injection, USP auto-injector, tell your healthcare provider about all your medical conditions, 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.

Epinephrine injection, USP auto-injector and other medicines may affect each other, causing side effects. Epinephrine injection, USP auto-injector may affect the way other medicines work, and other medicines may affect how epinephrine injection, USP auto-injector works.

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 epinephrine injection, USP auto-injector for treatment of anaphylaxis as prescribed by your healthcare provider, regardless of your medical conditions or the medicine you take.

### **How should I use epinephrine injection, USP auto-injector?**

- Each epinephrine injection, USP auto-injector contains only 1 dose of medicine.
- Epinephrine injection, USP auto-injector should only be injected into the middle of the outer thigh (upper leg). It can be injected through clothing, if needed.
- Read the Instructions for Use at the end of this Patient Information Leaflet for information about the right way to use epinephrine injection, USP auto-injector.
- Your healthcare provider will show you how to safely use the epinephrine injection, USP auto-injector.
- Use epinephrine injection, USP auto-injector exactly as your healthcare provider tells you to use it. You may need to use a second epinephrine injection, USP auto-injector 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 red tip. Never press or push the red tip with your thumb, fingers, or hand.** The needle comes out of the red tip. Accidental injection into finger, hands, or feet may cause a loss of blood flow to those 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 epinephrine injection, USP auto-injector comes packaged in a carton containing 1 or 2 epinephrine injection, USP auto-injectors.
- You may request a separate Trainer, that comes packaged with instructions. Additional video instructions on the use of epinephrine injection, USP auto-injector are available from [www.epinephrineautoinject.com](http://www.epinephrineautoinject.com). **The epinephrine injection, USP auto-injector Trainer has a beige color. The beige epinephrine injection, USP auto-injector Trainer contains no medicine and no needle.** Practice with your epinephrine injection, USP auto-injector Trainer before an allergic emergency happens to make sure you are able to safely use the real epinephrine injection, USP auto-injector in an emergency. Always carry your real epinephrine injection, USP auto-injector with you in case of an allergic emergency.
- Do not drop the carrying case or epinephrine injection, USP auto-injector. If the carrying case or epinephrine injection, USP auto-injector is dropped, check for damage and leakage. Dispose of the auto-injector and carrying case, and replace if damage or leakage is noticed or suspected.

### **What are the possible side effects of epinephrine injection, USP auto-injector?**

**Epinephrine injection, USP auto-injector may cause serious side effects.**

- **Epinephrine injection, USP auto-injector should only be injected into the middle of your outer thigh (upper leg). Do not** inject epinephrine injection, USP auto-injector into your:

- veins
- buttocks
- fingers, toes, hands or feet.

If you accidentally inject epinephrine injection, USP auto-injector 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 use epinephrine injection, USP auto-injector 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 epinephrine injection, USP auto-injector, 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 an injection.
- **If you have certain medical conditions, or take certain medicines, your condition may get worse or you may have more or longer lasting side effects when you use epinephrine injection, USP auto-injector.** Talk to your healthcare provider about all your medical conditions.

Common side effects of epinephrine injection, USP auto-injector include:

- faster, 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 epinephrine injection, USP auto-injector. 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 epinephrine injection, USP auto-injector?**

- Store epinephrine injection, USP auto-injector at room temperature between 68° to 77° F (20° to 25° C).
- Protect from light.
- **Do not** expose to extreme heat or cold. 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 viewing window of your auto-injector periodically. The solution should be clear. If the solution is discolored (pinkish or brown), cloudy or contains solid particles, replace the unit.

- Always keep your epinephrine injection, USP auto-injector in the carrying case to protect it from damage; however, the carrying case is not waterproof.
- The two blue end caps help to prevent accidental injection. Do not remove the blue end caps until you are ready to use epinephrine injection, USP auto-injector.
- Your epinephrine injection, USP auto-injector has an expiration date. Replace it before the expiration date.

**Keep epinephrine injection, USP auto-injector and all medicines out of the reach of children.**

**General information about the safe and effective use of epinephrine injection, USP auto-injector:**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use epinephrine injection, USP auto-injector for a condition for which it was not prescribed. Do not give epinephrine injection, USP auto-injector to other people.

This Patient Information Leaflet summarizes the most important information about epinephrine injection, USP auto-injector. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about epinephrine injection, USP auto-injector that is written for health professionals.

For more information and video instructions on the use of epinephrine injection, USP auto-injector, go to [www.epinephrineautoinject.com](http://www.epinephrineautoinject.com) or call 1-888-894-6528.

**What are the ingredients in epinephrine injection, USP auto-injector?**

**Active Ingredient:** epinephrine

**Inactive Ingredients:** sodium chloride, chlorobutanol, sodium bisulfite, hydrochloric acid and sodium hydroxide, and water.

**Important Information**

- **The epinephrine injection, USP auto-injector 0.3 mg auto-injector has a yellow colored label.**
- **The epinephrine injection, USP auto-injector 0.15 mg auto-injector has an orange colored label.**
- **The epinephrine injection, USP auto-injector Trainer has a beige color, and contains no medicine and no needle.**
- **Your auto-injector is designed to work through clothing.**
- **The two blue end caps on the epinephrine injection, USP auto-injector help to prevent accidental injection of the device. Do not remove the blue end caps 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 red tip. The needle comes out of the red tip.**
- **If an accidental injection happens, get medical help right away.**
- **Do not place patient information or any other foreign objects in carrier with the auto-injector, as this may prevent you from removing the auto-injector for use.**

**Instructions for Use**

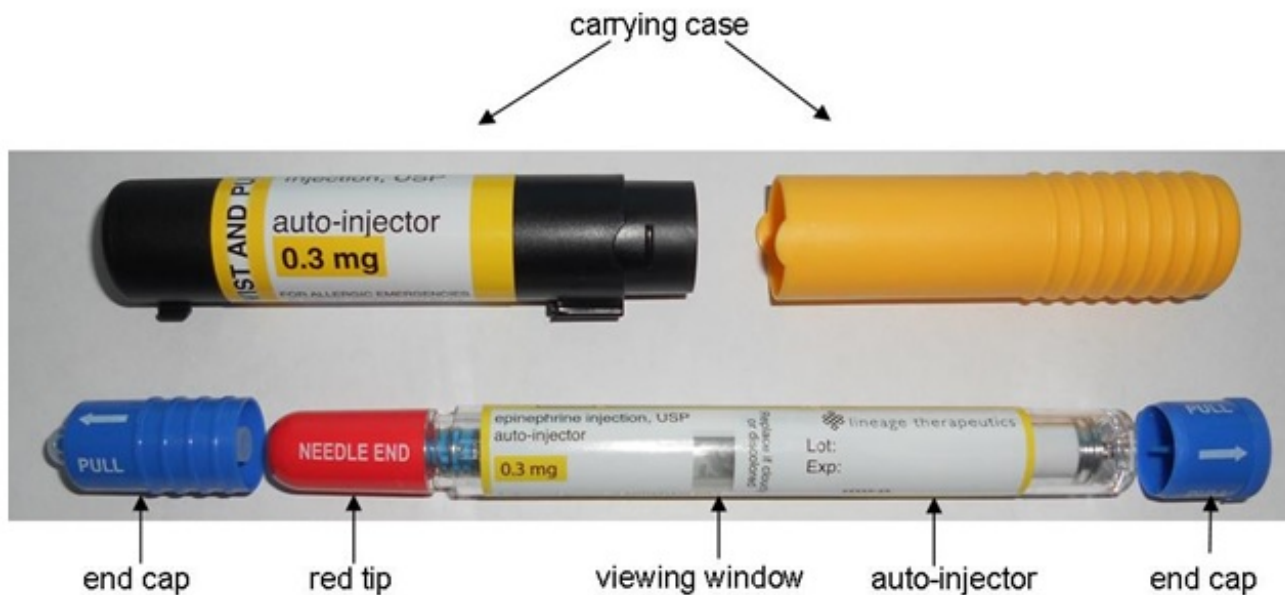
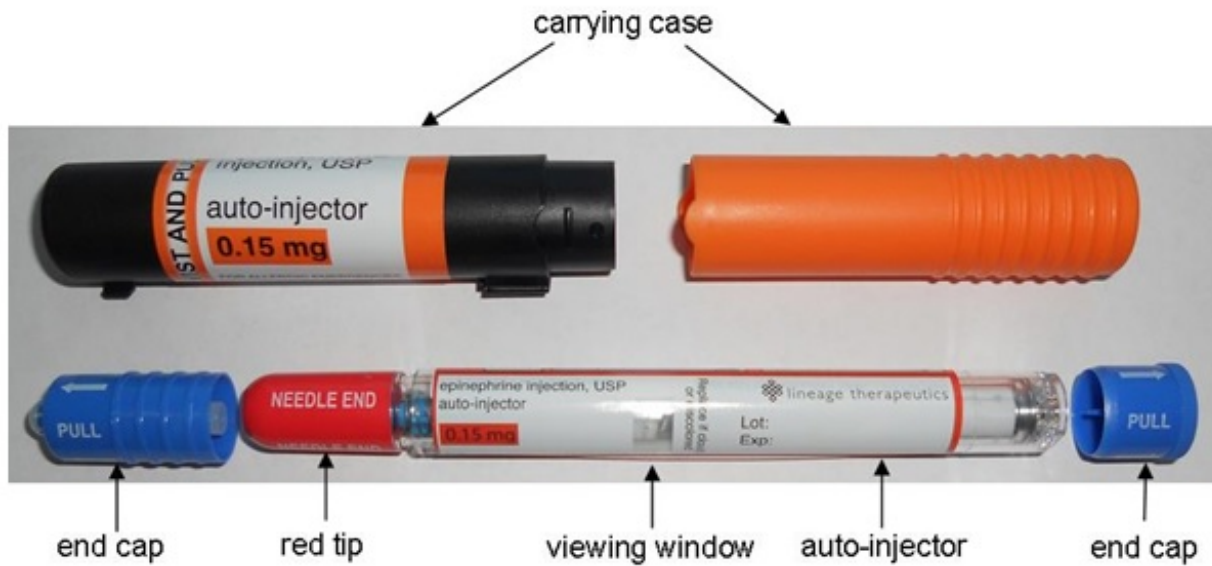
EPINEPHRINE INJECTION, USP AUTO-INJECTOR (ep-in-eph-rine)

For allergic emergencies (anaphylaxis)

Read these Instructions for Use carefully before you use epinephrine injection, USP auto-injector. Before you need to use your epinephrine injection, USP auto-injector, 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 epinephrine injection, USP auto-injector should also understand how to use it well. If you

have any questions, ask your healthcare provider.

## Your epinephrine injection, USP auto-injector

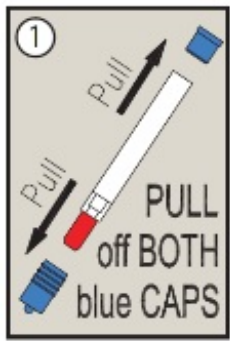


### STEP 1. Prepare epinephrine injection, USP auto-injector for injection

- Remove epinephrine injection, USP auto-injector from its protective carrying case.
- **Pull off blue end caps**; you will now see a red tip. Grasp the auto-injector in your fist with the red tip pointing downward. See **Figure A**.

#### Note:

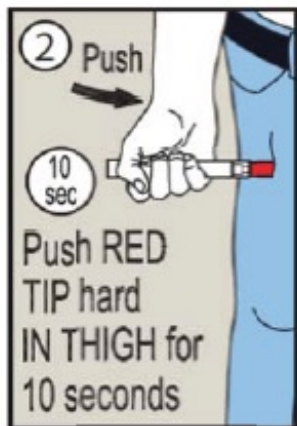
- The needle comes out of the red tip.
- To avoid an accidental injection, never put your thumb, fingers, or hand over the red tip. If an accidental injection happens, get medical help right away.



**Figure A**

**STEP 2. Administer epinephrine injection, USP auto-injector**

- If you are administering epinephrine injection, USP auto-injector to a young child, hold the leg firmly in place and limit movement prior to and while administering an injection.
- **Put the red tip against the middle of the outer thigh** (upper leg) at a 90° angle (perpendicular) to the thigh.
- **Press down hard and hold firmly against the thigh for approximately 10 seconds** to deliver the medicine. **See Figure B.**



**Figure B**

- Only inject into the middle of the outer thigh. **Do not** inject into any other part of the body.
- **Remove epinephrine injection, USP auto-injector from the thigh.**
- Massage the area for 10 seconds.
- **Check the red tip.** The injection is complete and you have received the correct dose of the medicine if you see the needle sticking out of the **red tip**. **If you do not see the needle repeat Step 2.**

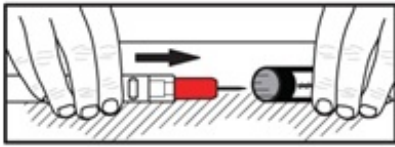
**STEP 3. Get emergency medical help right away.** You may need further medical attention. You may need to use a second epinephrine injection, USP auto-injector if symptoms continue or recur.

**STEP 4. After use / Disposal**

**Carefully cover the needle with the carrying case.**

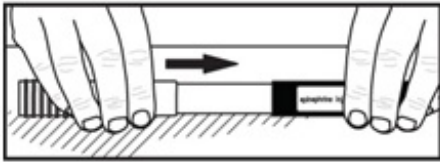
- Lay the labeled half of the carrying case cover down on a flat surface. Use one hand to carefully slide the end of the auto-injector, needle first, into the labeled carrying case cover. **See Figure C.**





**Figure C**

- After the needle is inside the labeled cover, push the unlabeled half of the carrying case cover firmly over the non-needle end of the auto-injector. **See Figure D.**



**Figure D**

- Take your used epinephrine injection, USP 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 epinephrine injection, USP auto-injector to the healthcare provider for inspection and proper disposal.
- Ask for a refill, if needed.

**Note:**

- Epinephrine injection, USP auto-injector is a single-use injectable device that delivers a fixed dose of epinephrine. The auto-injector cannot be reused. Do not attempt to reuse epinephrine injection, USP auto-injector 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 you see the needle sticking out of the **red** tip.
- A separate epinephrine injection, USP auto-injector Trainer is available. The epinephrine injection, USP auto-injector Trainer has a beige color. The beige epinephrine injection, USP auto-injector Trainer contains no medicine and no needle. Practice with your epinephrine injection, USP auto-injector Trainer, but always carry your real epinephrine injection, USP auto-injector in case of an allergic emergency.
- If you will be administering epinephrine injection, USP auto-injector 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 epinephrine injection, USP auto-injector apart.

For more information and video instructions on the use of epinephrine injection, USP auto-injector, go to [www.epinephrineautoinject.com](http://www.epinephrineautoinject.com) or call 1-888-894-6528.

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

05/2016

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Horsham, PA 19044

71007-08

**PRINCIPAL DISPLAY PANEL - 0.15 mg CARTON NDC 54505-101-02**

Rx Only

Lineage Therapeutics

epinephrine injection, USP

auto-injector

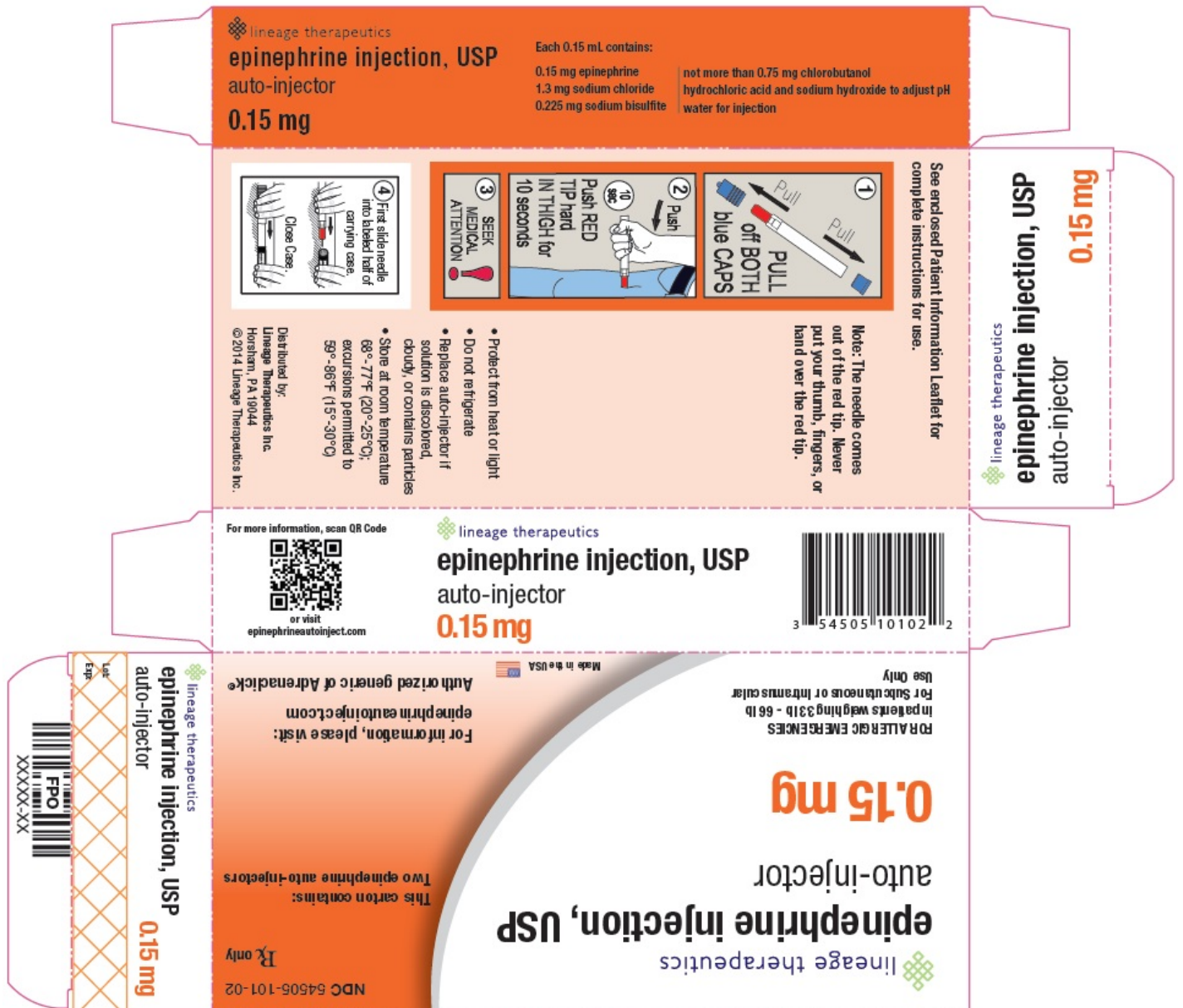
0.15 mg

For Allergic Emergencies

in patients weighing 33 lb – 66 lb

For Subcutaneous or Intramuscular Use Only

This carton contains: Two epinephrine auto-injectors



**PRINCIPAL DISPLAY PANEL - 0.15 mg WRAP LABEL**

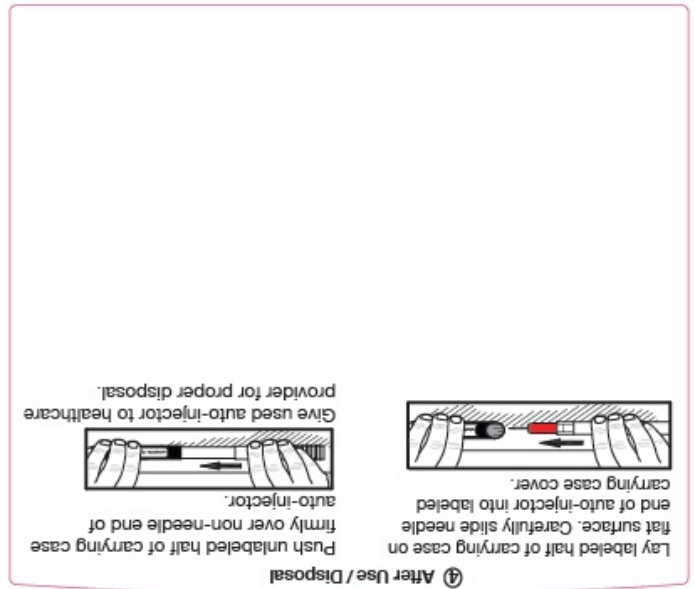
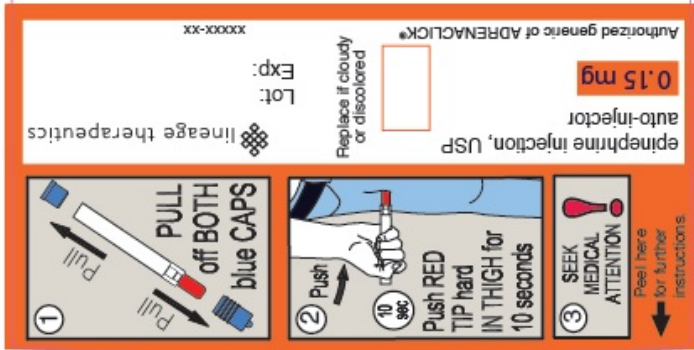
Lineage Therapeutics

epinephrine injection, USP

auto-injector

0.15 mg

**IMPORTANT:** Read Instructions for Use carefully before use  
 For intramuscular or subcutaneous use. For allergic emergencies (anaphylaxis).  
 Each 0.15 mL contains: 0.15 mg epinephrine, 1.3 mg sodium chloride,  
 0.225 mg sodium bisulfite, not more than 0.75 mg chlorobutanol.  
 Store at 20°C-25°C (68°F-77°F) with excursions permitted to 15°C-30°C (59°-86°F).  
 Protect from light. Do not refrigerate. Rx only  
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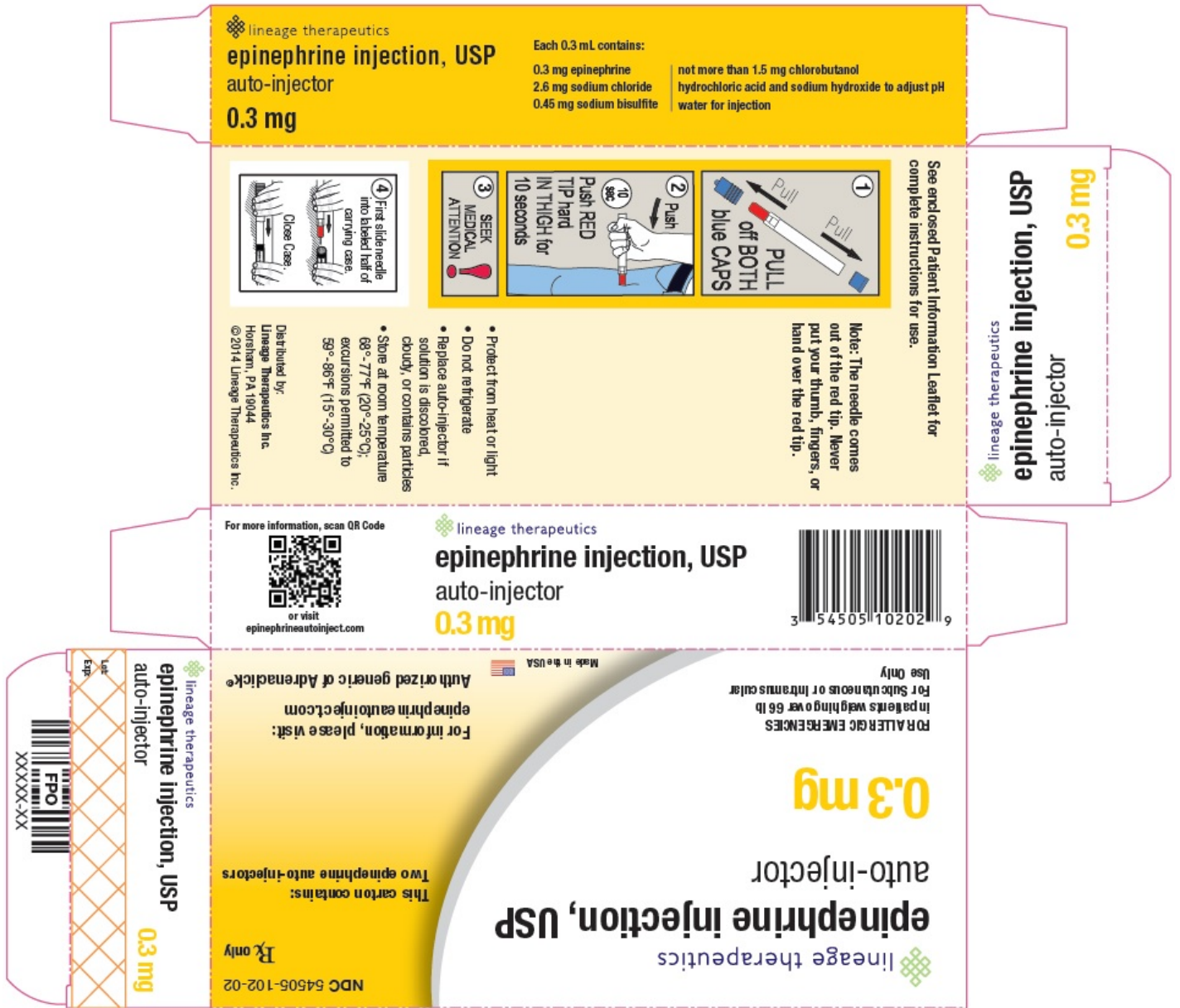
**PRINCIPAL DISPLAY PANEL - 0.15 mg CASE LABEL**

epinephrine injection, USP  
 auto-injector  
 0.15 mg  
 Lineage Therapeutics



**PRINCIPAL DISPLAY PANEL - 0.3 mg CARTON NDC 54505-102-02**

Rx Only  
 Lineage Therapeutics  
 epinephrine injection, USP  
 auto-injector  
 0.3 mg  
 For Allergic Emergencies  
 in patients weighing over 66 lb  
 For Subcutaneous or Intramuscular Use Only  
 This carton contains: Two epinephrine auto-injectors

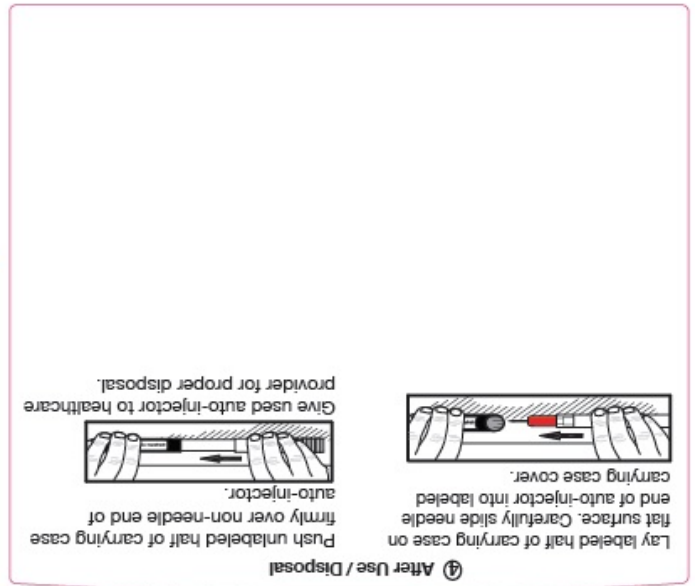
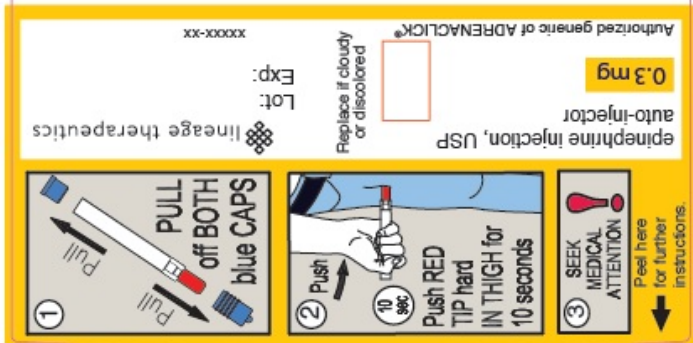


**PRINCIPAL DISPLAY PANEL - 0.3 mg WRAP LABEL**

Lineage Therapeutics  
 epinephrine injection, USP  
 auto-injector  
 0.3 mg



**IMPORTANT:** Read Instructions for Use carefully before use  
 For intramuscular or subcutaneous use. For allergic emergencies (anaphylaxis).  
 Each 0.3 mL contains: 0.3 mg epinephrine, 2.6 mg sodium chloride,  
 0.45 mg sodium bisulfite, not more than 1.5 mg chlorobutanol.  
 Store at 20°C-25°C (68°F-77°F) with excursions permitted to 15°C-30°C (59°-86°F).  
 Protect from light. Do not refrigerate. Rx only  
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**PRINCIPAL DISPLAY PANEL - 0.3 mg CASE LABEL**

epinephrine injection, USP  
 auto-injector  
 0.3 mg  
 Lineage Therapeutics



**EPINEPHRINE**

epinephrine injection

**Product Information**

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:54505-101
<b>Route of Administration</b>	SUBCUTANEOUS		

**Active Ingredient/Active Moiety**

Ingredient Name		Basis of Strength	Strength	
EPINEPHRINE (UNII: YKH834O4BH) (EPINEPHRINE - UNII:YKH834O4BH)		EPINEPHRINE	0.15 mg in 0.15 mL	
<b>Inactive Ingredients</b>				
Ingredient Name		Strength		
SODIUM CHLORIDE (UNII: 451W47IQ8X)				
CHLOROBUTANOL (UNII: HM4YQM8WRC)				
SODIUM BISULFITE (UNII: TZX5469Z6I)				
HYDROCHLORIC ACID (UNII: QTT17582CB)				
SODIUM HYDROXIDE (UNII: 55X04QC32I)				
<b>Packaging</b>				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54505-101-01	1 in 1 CARTON	04/01/2010	
1		1 in 1 CASE		
1		0.15 mL in 1 SYRINGE, GLASS; Type 0: Not a Combination Product		
2	NDC:54505-101-02	2 in 1 CARTON	04/01/2010	
2		1 in 1 CASE		
2		0.15 mL in 1 SYRINGE, GLASS; Type 0: Not a Combination Product		
<b>Marketing Information</b>				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA AUTHORIZED GENERIC	NDA020800	04/01/2010		

EPINEPHRINE			
epinephrine injection			
<b>Product Information</b>			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54505-102
Route of Administration	SUBCUTANEOUS		
<b>Active Ingredient/Active Moiety</b>			
Ingredient Name		Basis of Strength	Strength
EPINEPHRINE (UNII: YKH834O4BH) (EPINEPHRINE - UNII:YKH834O4BH)		EPINEPHRINE	0.3 mg in 0.3 mL
<b>Inactive Ingredients</b>			
Ingredient Name		Strength	

<b>SODIUM CHLORIDE</b> (UNII: 451W47IQ8X)	
<b>CHLOROBUTANOL</b> (UNII: HM4YQM8WRC)	
<b>SODIUM BISULFITE</b> (UNII: TZX5469Z6I)	
<b>HYDROCHLORIC ACID</b> (UNII: QTT17582CB)	
<b>SODIUM HYDROXIDE</b> (UNII: 55X04QC32I)	

<b>Packaging</b>				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54505-102-01	1 in 1 CARTON	04/01/2010	
1		1 in 1 CASE		
1		0.3 mL in 1 SYRINGE, GLASS; Type 0: Not a Combination Product		
2	NDC:54505-102-02	2 in 1 CARTON	04/01/2010	
2		1 in 1 CASE		
2		0.3 mL in 1 SYRINGE, GLASS; Type 0: Not a Combination Product		

<b>Marketing Information</b>			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC	NDA020800	04/01/2010	

**Labeler** - Lineage Therapeutics Inc (078677620)

Revised: 5/2016

Lineage Therapeutics Inc