HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ADRENACLICK® safely and effectively. See full prescribing information for ADRENACLICK.

ADRENACLICK® (epinephrine injection, USP) 0.3 mg, 0.15 mg Auto-Injector, 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

Adrenaclick 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): Adrenaclick 0.3 mg (2)
- Patients 15 to 30 kg (33 lbs-66 lbs): Adrenaclick 0.15 mg (2)

Inject Adrenaclick 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 Amedra Pharmaceuticals LLC at 1-888-894-6528 or FDA at 1-800-FDA-1088 or *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*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Emergency Treatment
5.2 Injection-Related Complications
5.3 Serious Infections at the Injection Site
5.4 Allergic Reactions Associated with Sulfite
5.5 Disease Interactions
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

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

Reference ID: 3932620

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Adrenaclick® 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.

Adrenaclick 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.

Adrenaclick 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 Adrenaclick dosage strength is determined according to patient body weight.

- Patients greater than or equal to 30 kg (approximately 66 pounds or more): Adrenaclick 0.3 mg
- Patients 15 to 30 kg (33 pounds to 66 pounds): Adrenaclick 0.15 mg

Inject Adrenaclick intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Instruct caregivers of young children who are prescribed an Adrenaclick 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 Adrenaclick contains a single dose of epinephrine for single use injection. Since the doses of epinephrine delivered from Adrenaclick 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 Adrenaclick may be necessary. More than two sequential doses of epinephrine should only be administered under direct medical supervision [see *Warnings and Precautions (5.1)*].

Reference ID: 3932620

The epinephrine solution in the viewing window of Adrenaclick 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

Adrenaclick 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

Adrenaclick 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.

Reference ID: 3932620

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 Adrenaclick 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 Adrenaclick 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 Adrenaclick to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

Reference ID: 3932620

- 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 Adrenaclick 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)*].

Reference ID: 3932620

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, tripelennamine, and diphenhydramine.

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

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

Ergot alkaloids may also reverse the pressor effects of epinephrine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

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

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

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

Reference ID: 3932620

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 Adrenaclick is administered to a nursing woman.

8.4 Pediatric Use

Adrenaclick 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 Adrenaclick 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, Adrenaclick 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

Adrenaclick (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.

Reference ID: 3932620

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

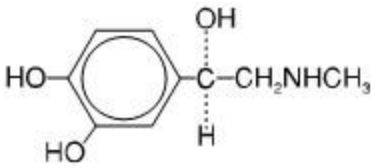
Each Adrenaclick 0.15 mg delivers a single dose of 0.15 mg epinephrine from epinephrine injection, USP (0.15 mL) in a sterile solution.

Adrenaclick 0.3 mg and Adrenaclick 0.15 mg each contain 1.1 mL of epinephrine solution. 0.3 mL and 0.15 mL epinephrine solution are dispensed for Adrenaclick 0.3 mg and Adrenaclick 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 Adrenaclick 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 Adrenaclick 0.15 mg contains 0.15 mg epinephrine, 1.3 mg sodium chloride, not more than 0.75 mg chlorobutanol, 0.225 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-α-[(methylamino)methyl]benzyl alcohol with the following structure:



Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. Replace Adrenaclick if the epinephrine solution appears discolored (pinkish or brown color), cloudy, or contains particles.

Thoroughly review the patient instructions and operation of Adrenaclick 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.

Reference ID: 3932620

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 Adrenaclick (epinephrine injection, USP) 0.3 mg auto-injectors:
NDC 52054-804-02.

Carton containing two Adrenaclick (epinephrine injection, USP) 0.15 mg auto-injectors:
NDC 52054-803-02.

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)*]

Reference ID: 3932620

A healthcare provider should review the patient instructions and operation of Adrenaclick, 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 Adrenaclick. Adrenaclick 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 Adrenaclick has been injected into the thigh of young children who are uncooperative and kick during an injection [see *Warnings and Precautions (5.2)*].

Each Adrenaclick is a single-use injection. Advise patients to seek immediate medical care in conjunction with administration of Adrenaclick.

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

Reference ID: 3932620

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 Adrenaclick 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 Adrenaclick 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 Adrenaclick auto-injector carton.

Manufactured for and Distributed by: Amedra Pharmaceuticals LLC, Horsham, PA 19044

© 2014 Amedra Pharmaceuticals LLC, Horsham, PA. All rights reserved.

For inquiries call 1-888-894-6528

51006-07

Reference ID: 3932620

Patient Information

ADRENACLICK® (a-dren-a-click)

(epinephrine injection, USP)

Auto-Injector

For allergic emergencies (anaphylaxis)

Read this Patient Information Leaflet carefully before you use the Adrenaclick 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 Adrenaclick 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 Adrenaclick?

1. Adrenaclick 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)

Reference ID: 3932620

2. **Always carry your Adrenaclick 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 Adrenaclick 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 Adrenaclick right away.**
   - **Get emergency medical help right away**. You may need further medical attention. You may need to use a second Adrenaclick 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 Adrenaclick?

- Adrenaclick 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.
- Adrenaclick 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 Adrenaclick.
- Adrenaclick is for people who have been prescribed this medicine by their healthcare provider.
- The Adrenaclick 0.3 mg auto-injector is for patients who weigh 66 pounds or more (30 kilograms or more).
- The Adrenaclick 0.15 mg auto-injector is for patients who weigh about 33 to 66 pounds (15 to 30 kilograms).
- It is not known if Adrenaclick is safe and effective in children who weigh less than 33 pounds (15 kilograms).

What should I tell my healthcare provider before using Adrenaclick?

Before you use Adrenaclick, 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.

Adrenaclick and other medicines may affect each other, causing side effects. Adrenaclick may affect the way other medicines work, and other medicines may affect how Adrenaclick 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 Adrenaclick 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 Adrenaclick?

- Each Adrenaclick auto-injector contains only 1 dose of medicine.
- Adrenaclick 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 Adrenaclick.
- Your healthcare provider will show you how to safely use the Adrenaclick auto-injector.
- Use Adrenaclick exactly as your healthcare provider tells you to use it. You may need to use a second Adrenaclick 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 Adrenaclick auto-injector comes packaged in a carton containing 2 Adrenaclick auto-injectors.

Reference ID: 3932620

- You may request a separate Trainer, that comes packaged with instructions. Additional video instructions on the use of Adrenaclick are available from www.adrenaclick.com. **The Adrenaclick Trainer has a beige color. The beige Adrenaclick Trainer contains no medicine and no needle.** Practice with your Adrenaclick Trainer before an allergic emergency happens to make sure you are able to safely use the real Adrenaclick auto-injector in an emergency. Always carry your real Adrenaclick auto-injector with you in case of an allergic emergency.
- Do not drop the carrying case or Adrenaclick auto-injector. If the carrying case or Adrenaclick 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 Adrenaclick?

Adrenaclick may cause serious side effects.

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

  If you accidently inject Adrenaclick 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 Adrenaclick 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 Adrenaclick, 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**

Reference ID: 3932620

effects when you use Adrenaclick. Talk to your healthcare provider about all your medical conditions.

Common side effects of Adrenaclick 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 Adrenaclick. 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 Adrenaclick?

- Store Adrenaclick 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 Adrenaclick 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 Adrenaclick.
- Your Adrenaclick has an expiration date. Replace it before the expiration date.

Keep Adrenaclick and all medicines out of the reach of children.

Reference ID: 3932620

General information about the safe and effective use of Adrenaclick:

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

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

For more information and video instructions on the use of Adrenaclick, go to www.adrenaclick.com or call 1-888-894-6528.

What are the ingredients in Adrenaclick?

Active Ingredient: epinephrine

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

Important Information

- **The Adrenaclick 0.3 mg auto-injector has a yellow colored label.**
- **The Adrenaclick 0.15 mg auto-injector has an orange colored label.**
- **The Adrenaclick 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 Adrenaclick 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.**

Reference ID: 3932620

Instructions for Use

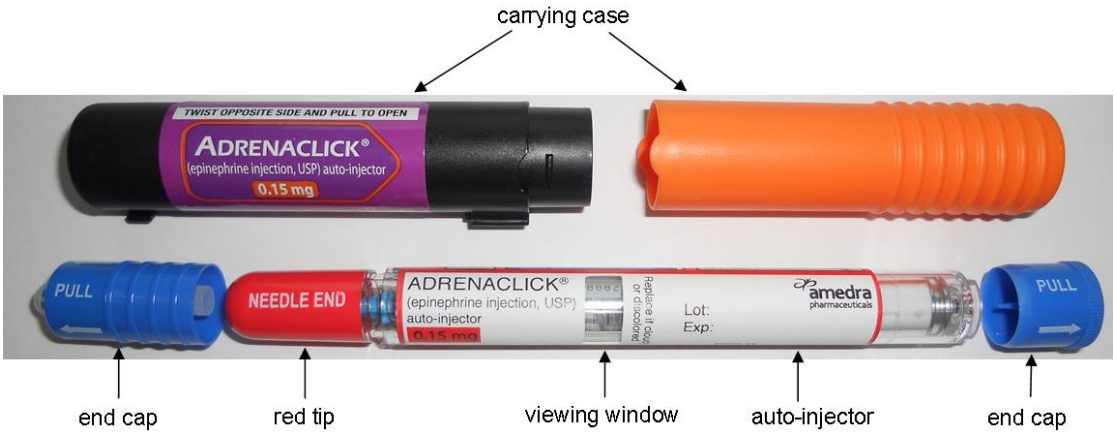
ADRENACLICK® (a-dren-a-click)

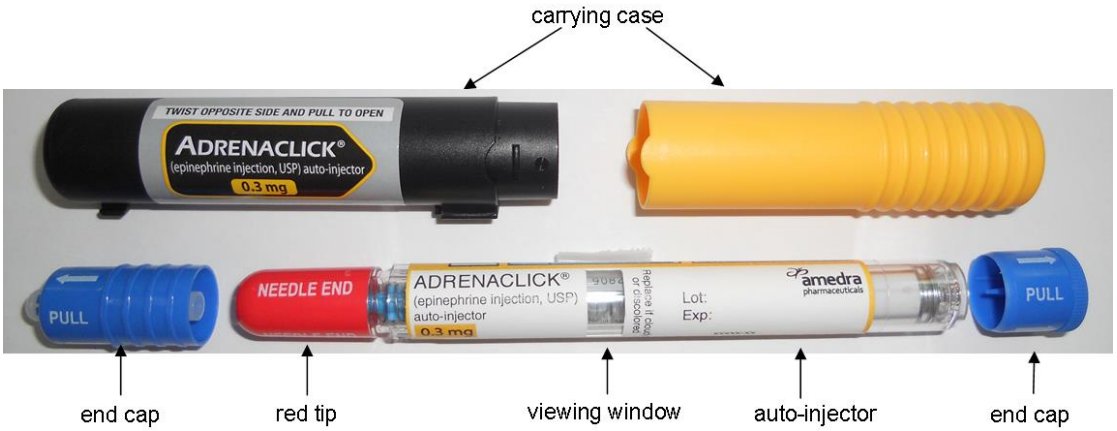
(epinephrine injection, USP) Auto-Injector

For allergic emergencies (anaphylaxis)

Read these Instructions for Use carefully before you use Adrenaclick. Before you need to use your Adrenaclick, 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 Adrenaclick auto-injector should also understand how to use it well. If you have any questions, ask your healthcare provider.

Your Adrenaclick auto-injector





STEP 1. Prepare Adrenaclick for injection

- Remove Adrenaclick 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.

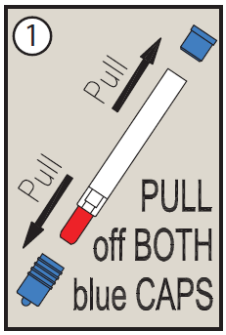


Figure A

STEP 2. Administer Adrenaclick

- If you are administering Adrenaclick 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.**

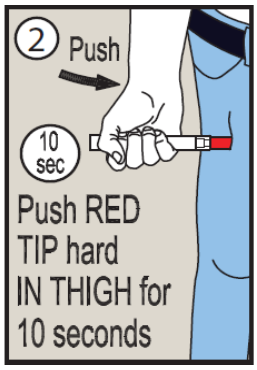


Figure B

- Only inject into the middle of the outer thigh. **Do not** inject into any other part of the body.
- **Remove Adrenaclick 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 Adrenaclick 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.**

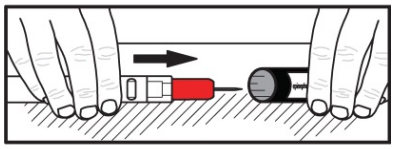


Figure C

- 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.**

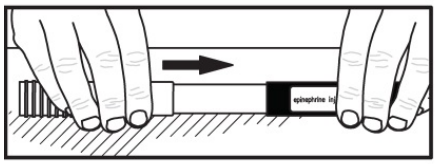


Figure D

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

Note:

- Adrenaclick is a single-use injectable device that delivers a fixed dose of epinephrine. The auto-injector cannot be reused. Do not attempt to reuse Adrenaclick 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.

Reference ID: 3932620

- A separate Adrenaclick Trainer is available. The Adrenaclick Trainer has a beige color. The beige Adrenaclick Trainer contains no medicine and no needle. Practice with your Adrenaclick Trainer, but always carry your real Adrenaclick auto-injector in case of an allergic emergency.
- If you will be administering Adrenaclick 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 Adrenaclick auto-injector apart.

For more information and video instructions on the use of Adrenaclick, go to www.adrenaclick.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

© 2014 Amedra Pharmaceuticals LLC, Horsham, PA. All rights reserved.

Manufactured for and Distributed by:
Amedra Pharmaceuticals LLC
Horsham, PA 19044

51007-07

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*.

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*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Emergency Treatment
5.2 Injection-Related Complications
5.3 Serious Infections at the Injection Site
5.4 Allergic Reactions Associated with Sulfite
5.5 Disease Interactions
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

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

Reference ID: 3932620

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.

Reference ID: 3932620

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

Reference ID: 3932620

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

Reference ID: 3932620

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)*].

Reference ID: 3932620

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, tripelennamine, and diphenhydramine.

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

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

Ergot alkaloids may also reverse the pressor effects of epinephrine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

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

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

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

Reference ID: 3932620

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.

Reference ID: 3932620

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.

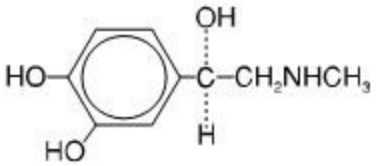
Each epinephrine injection, USP auto-injector 0.15 mg delivers a single dose of 0.15 mg epinephrine from epinephrine injection, USP (0.15 mL) in a sterile solution.

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 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-α-[(methylamino)methyl]benzyl alcohol with the following structure:



Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. Replace epinephrine injection, 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.

Reference ID: 3932620

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.

Reference ID: 3932620

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

Reference ID: 3932620

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

© 2014 Lineage Therapeutics Inc., Horsham, PA. All rights reserved.

For inquiries call 1-888-894-6528

71006-08

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)

Reference ID: 3932620

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. **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 accidently 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 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.**

Reference ID: 3932620

- **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.**

Reference ID: 3932620

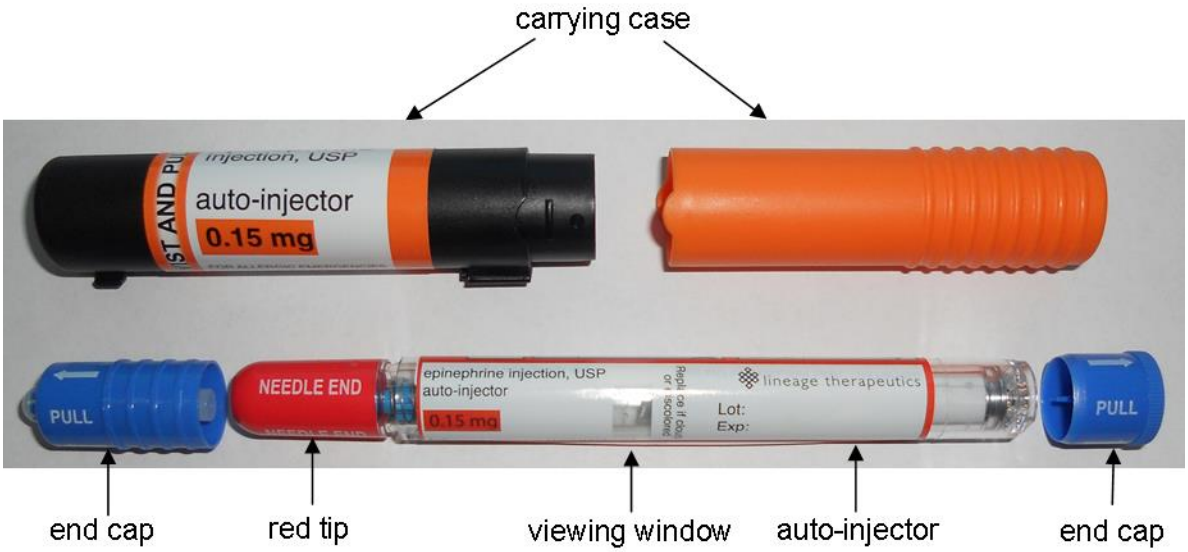
Instructions for Use

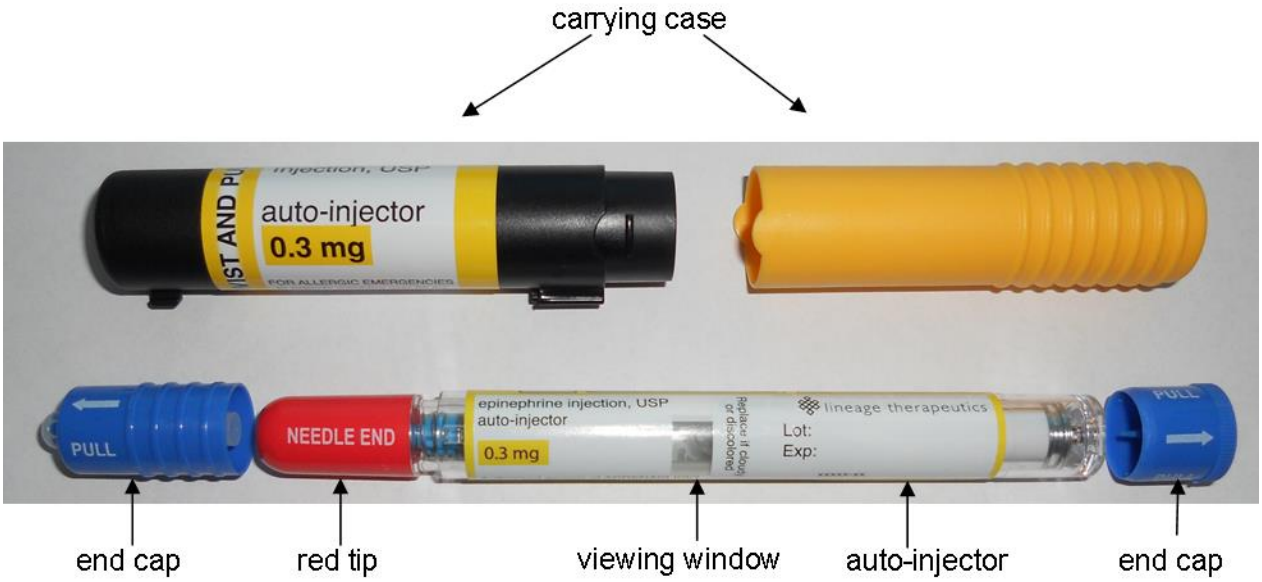
EPINEPHRINE INJECTION, USP AUTO-INJECTOR (ep-in-eph-rine)

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.

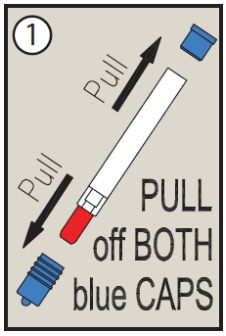


Figure A

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.**

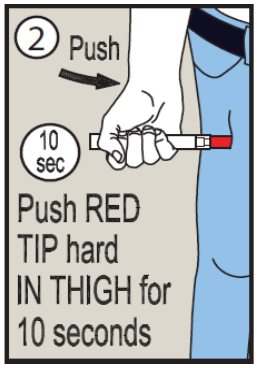


Figure B

- 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.**

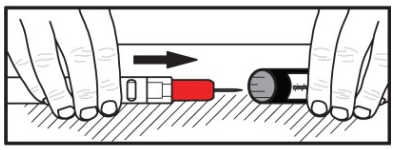


Figure C

- 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.**

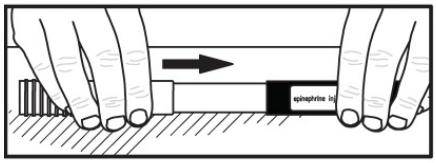


Figure D

- 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 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

© 2014 Lineage Therapeutics Inc., Horsham, PA. All rights reserved.

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

71007-08

Twinject®
auto-injector
(epinephrine injection, USP 1:1000)
Available as: 0.3 mg 0.15 mg
each dose delivers 0.15 mg or 0.3 mg of epinephrine

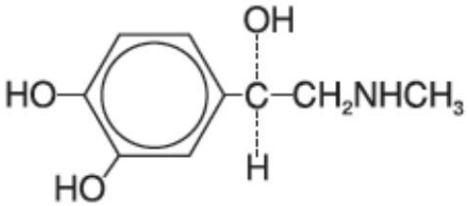
DESCRIPTION

Twinject auto-injector contains 1.1 mL epinephrine injection, USP 1mg/mL (1:1000), from which two doses of either 0.15 mg (0.15 mL) or 0.3 mg (0.3 mL) each are available for use by injection. The first dose is administered by auto-injection after the patient prepares and fires Twinject as directed. A second dose can be manually administered following a partial disassembly of Twinject. The remaining volume is not available for use and should be discarded. See PATIENT DIRECTIONS FOR USE on the accompanying Patient Information Leaflet.

Each dose of epinephrine injection, USP 1:1000 contains either 0.15 mg or 0.3 mg l-epinephrine, sodium chloride, chlorobutanol and sodium bisulfite, all sealed under nitrogen.

Epinephrine is a sympathomimetic catecholamine. Its naturally occurring l-isomer, which is twenty times as active as the d-isomer, is obtained in pure form by separation from the synthetically produced racemate.

Chemically, epinephrine is 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol with the following structure:



Epinephrine deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. Epinephrine solutions that show evidence of discoloration should be discarded.

Twinject contains no latex.

CLINICAL PHARMACOLOGY

Epinephrine is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to allergens, such as those present in certain insect venoms, foods, or drugs. It can also be used in the treatment of anaphylaxis of unknown cause (idiopathic anaphylaxis) or exercise-induced anaphylaxis. Epinephrine, when given intramuscularly or subcutaneously, has a rapid onset and short duration of action. Epinephrine acts on both alpha and beta adrenergic receptors. Through its action on alpha adrenergic receptors, epinephrine lessens the vasodilation and increased vascular permeability that occurs during an anaphylactic reaction and can lead to loss of intravascular fluid volume and hypotension. Through its action on beta adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation that helps alleviate bronchospasm,

wheezing, and dyspnea that may occur during anaphylaxis. Epinephrine also helps alleviate pruritus, urticaria, and angioedema, and may be effective in relieving gastrointestinal and genitourinary symptoms of anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus and urinary bladder.

INDICATIONS AND USAGE

Twinject (epinephrine injection, USP 1:1000) is indicated in the emergency treatment of severe 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 anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis. Twinject is intended for immediate administration in patients with a history of anaphylactic reactions. Selection of the appropriate dosage strength is determined according to patient body weight (See DOSAGE AND ADMINISTRATION section).

Such reactions may occur within minutes after exposure 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. Twinject is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical care.

CONTRAINDICATIONS

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

WARNINGS

Injection-Related Complications.

Twinject should only be injected into the anterolateral aspect of the thigh. Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided.

Do not injection 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 this risk.

Avoid possible inadvertent intravascular administration. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to a sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.

If there is an accidental injection into these areas, advise the patient to inform the healthcare provider of the accidental injection when he/she goes to the nearest emergency room for further treatment of anaphylaxis.

Hold the 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 Twinject to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

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 Twinject 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.

Allergic Reactions Associated with Sulfite. 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. 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.

Disease Interactions. Epinephrine should be administered with caution to patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In patients with coronary insufficiency or ischemic heart disease, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. It should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.

Epinephrine is light sensitive and should be stored in the carrying-case provided. Store at room temperature (20º-25ºC/68º-77ºF) with excursions permitted to 15º-30ºC (59º-86ºF). Do not refrigerate; protect from freezing. Patients should periodically check the solution in Twinject for any discoloration and/or precipitates. If the solution is discolored or contains a precipitate, the patient should replace their Twinject.

PRECAUTIONS

(1) General

Twinject is not intended as a substitute for immediate medical care. In conjunction with the administration of epinephrine, the patient should seek appropriate medical care. More than two sequential doses of epinephrine should only be administered under direct medical supervision.

Twinject is not suitable for patients, or caregivers, with such disabilities as severe debilitating arthritis of the hands, because the use of this product requires some manual dexterity to administer. IN ALL CASES, THE PHYSICIAN SHOULD INSTRUCT THE PATIENT AND/OR ANY OTHER PERSON WHO MIGHT BE IN A POSITION TO ADMINISTER THE EPINEPHRINE, IN THE PROPER USE OF Twinject.

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions should be instructed about the circumstances under which epinephrine should be used (See INDICATIONS AND USAGE Section). It should be determined that the patient is at risk of future anaphylaxis, since there are some concerns in specific patients with epinephrine administration. (a) Epinephrine should be used with caution in patients with cardiac arrhythmias, coronary artery or organic heart disease, hypertension, or in patients who are on medications that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, or anti-arrhythmics. In such patients, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. (b) The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors. (c) Some patients may be at greater risk of developing adverse reactions after epinephrine administration. These include patients with hyperthyroidism, cardiovascular disease, hypertension, diabetes, and elderly individuals, and pregnant women. It must be noted that, despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions, or any other person who might be in a position to administer epinephrine to a patient with these conditions experiencing anaphylaxis, should be instructed about the circumstances under which epinephrine should be used.

(2) Information for Patients

Complete patient information, including dosage, directions for proper administration, and precautions, can be found inside each Twinject package within the Patient Information Leaflet.

Epinephrine may produce symptoms and signs that include an increase in pulse rate, the sensation of a more forceful heartbeat, palpitations, a throbbing headache, pallor, feelings of overstimulation, anxiety, weakness, shakiness, dizziness, or nausea. 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.

(3) Drug Interactions

Patients who receive epinephrine while concomitantly taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

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

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

(4) Carcinogenesis, Mutagenesis, Impairment of Fertility
There are no data from either animal or human studies regarding the carcinogenicity or mutagenicity of epinephrine, and no studies have been conducted to determine its potential for the impairment of fertility. This should not prevent the use of epinephrine under the conditions noted under INDICATIONS AND USAGE section.

(5) Pregnancy
Pregnancy Category C. Epinephrine has been shown to have developmental effects in rabbits at a subcutaneous dose of 1.2 mg/kg (approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), in mice at a subcutaneous dose of 1 mg/kg (approximately 7 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), and in hamsters at a subcutaneous dose of 0.5 mg/kg (approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). Although there are no adequate and well-controlled studies in pregnant women, epinephrine crosses the placenta and could lead to fetal anoxia, spontaneous abortion or both. Therefore, epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS
Adverse reactions to epinephrine include transient, moderate 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. Large doses of epinephrine can cause acute hypertension. Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs [see (3) Drug Interactions]. Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. The potential for epinephrine to produce these types of adverse reactions does not contraindicate its use in an acute, life-threatening allergic reaction.

Lacerations, bent needles, and embedded needles have been reported when Twinject has been injected into the thigh of young children who are uncooperative and kick or move during an injection.

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.

OVERDOSAGE

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

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

If an epinephrine overdose induces pulmonary edema that interferes with respiration, treatment consists of a rapidly acting alpha-adrenergic blocking drug 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.

DOSAGE AND ADMINISTRATION

The physician who prescribes Twinject should review this Prescribing Information insert in detail with the patient. This review should include the proper use of Twinject to ensure that subcutaneous or intramuscular injections are given into the anterolateral aspect of the thigh, through clothing if necessary. Instruct caregivers of young children who are prescribed Twinject 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. The accompanying Patient Information Leaflet and Wrap Label should also be reviewed with the patient.

Twinject is capable of delivering two doses of either 0.15 mg or 0.3 mg (0.15 mL or 0.3 mL of 1:1000 dilution of epinephrine) each. The first dose is available for auto-injection by the patient, and the second dose is available for manual injection by the patient following a partial disassembly of Twinject.

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

Twinject 0.15 mg	For use by patients who weigh 15 - 30 kilograms (approximately 33 - 66 pounds)
Twinject 0.3 mg	For use by patients who weigh 30 kilograms (approximately 66 pounds) or greater

The usual dose of epinephrine for allergic emergencies in patients who weigh 30 kilograms or greater is 0.3 mg (0.3 mL of 1:1000 dilution of epinephrine).

Since the doses of epinephrine delivered from Twinject are fixed, the physician should consider other forms of injectable epinephrine if doses lower than those available from Twinject are felt to be necessary. The prescribing physician 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 being prescribed.

Patients should be instructed to periodically visually inspect the epinephrine solution for particulate matter and discoloration. If the solution contains particulate matter or develops a pinkish color or becomes darker than slightly yellow, the patient should immediately contact their physician for a replacement, since these changes indicate that the effectiveness of the drug product may be decreased.

HOW SUPPLIED

Twinject is a patient (or caregiver) actuated, dual-dose product that contains 1.1 mL of epinephrine injection, USP (1:1000 or 1 mg/mL), of which an initial dose can be delivered by auto-injection, and a second dose is available by manual administration. THE REMAINING VOLUME THAT IS LEFT AFTER THESE TWO FIXED DOSES CANNOT BE FURTHER ADMINISTERED AND SHOULD BE DISCARDED WITH THE DEVICE AS OUTLINED IN THE PATIENT INFORMATION LEAFLET.

Twinject 0.15 mg is available in a single unit carton, NDC XXXXX-XXX-XX, and in a Two-Pack, NDC XXXXX-XXX-XX, containing two Twinject 0.15 mg auto-injectors and one Twinject Demonstrator.

Twinject 0.3 mg is available in a single unit carton, NDC XXXXX-XXX-XX, and in a Two-Pack, NDC XXXXX-XXX-XX, containing two Twinject 0.3 mg auto-injectors and one Twinject Demonstrator.

PROTECT FROM LIGHT. STORE AT ROOM TEMPERATURE, 20°-25°C (68°-77°F) WITH EXCURSIONS PERMITTED TO 15°-30°C (59°-86°F). PROTECT FROM FREEZING. DO NOT REFRIGERATE.

Rx only.

Manufactured for and Distributed by: Amedra Pharmaceuticals LLC, Horsham, PA 19044

© 2014 Amedra Pharmaceuticals LLC, Horsham, PA. All rights reserved.

For inquiries call X-XXX-XXXX-XXX

Revised May 2016

Twinject® auto-injector
(epinephrine injection, USP 1:1000)
Available as: 0.3 mg 0.15 mg

Patient Information

The patient, and caregiver, if possible, should read this information carefully before using Twinject® (TWIN-jehkt). You must know how to use Twinject before you have an emergency. This information contains additional details beyond the quick-reference instructions on the Twinject label. This information does not replace talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Twinject?

Use Twinject and go to your doctor or emergency room right away for more medical treatment.

• Epinephrine, the active ingredient in Twinject helps treat life-threatening allergic reactions.
• Make sure to tell your doctor about all your medical conditions and allergies.
• Always get medical treatment right away after using Twinject.

Since you cannot predict when a life-threatening allergic reaction will occur, carry Twinject with you at all times.

Look at the medicine in your Twinject regularly. If it looks cloudy (has particles in it), is discolored, or if the expiration date has passed, the Twinject should be replaced. In the event of a life-threatening allergic reaction, you should go ahead and use an out-of-date product, if that is all you have.

After the first and second dose, liquid will remain in the syringe that can't be used and should be discarded with the syringe as outlined in this Patient Information Leaflet.

What is Twinject?

Twinject is an emergency injection ("shot") of epinephrine. It is a medicine used for life-threatening allergic reactions such as severe swelling, breathing problems, or loss of blood pressure. Allergic reactions can be caused by stinging and biting insects (bugs), allergy injections, food, medicines, exercise, or unknown causes.

Life-threatening allergic reactions may show up as closing of your breathing airways, wheezing, sneezing, hoarseness, hives, itching, swelling, skin redness, fast heartbeat, weak pulse, feeling very anxious, confusion, stomach pain, losing control of urine or bowel movements (incontinence), faintness, or "passing out" (unconsciousness).

• Each Twinject can give 2 injections.

• Twinject 0.15mg is for patients who weigh 33-66 pounds (15-30 kg).
• Twinject 0.3mg is for patients who weigh 66 pounds (30 kg) or greater.
• Use of Twinject must be followed by emergency medical care.

Who should not use Twinject?

There are no absolute contraindications to the use of Twinject in a life-threatening allergic reaction. People with certain medical conditions have a higher chance of getting serious side effects from Twinject.

Tell your doctor about all your medical conditions, but especially if you:
• have heart disease or high blood pressure
• have diabetes
• have thyroid conditions
• have asthma
• have depression or other mental disease
• have Parkinson's disease
• are pregnant
• are allergic to any of the ingredients in Twinject

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Some medicines may cause serious side effects if taken while you use Twinject. Some medicines may affect how Twinject works, or Twinject may affect how your other medicines work. Diabetic patients may need to adjust the dose of their diabetes medicines or insulin after using Twinject.

How should I use Twinject?

• **Do <u>NOT</u> remove the green caps until you are ready to use.**
• **Never put thumb, fingers, or hand over the red tip.** The needle comes out of the red tip. Accidental injection into hand or feet may result in the loss of blood flow to these areas. If this happens, go immediately to the nearest emergency room.
• Hold Twinject in the thigh while slowly counting to 10 to make sure all medicine is delivered.
• Twinject is not suitable for patients, or caregivers, with such disabilities as severe debilitating arthritis of the hands, because the use of this product requires some manual dexterity to administer.
• Inject Twinject only into the middle of the outer side of your thigh (upper leg).
• Instructions on how to use Twinject also can be found at www.xxxxx.xxx.

What should I avoid while using Twinject?

• Avoid injecting Twinject into your buttock or any other part of your body, other than the middle of the outer side of your thigh (upper leg).
• Avoid injecting Twinject into a vein.

What are the possible side effects of Twinject?

Too much epinephrine (Twinject) can cause dangerously high blood pressure, stroke, or death.

If you take certain medicines, you may develop serious life-threatening side effects from the epinephrine in Twinject. Be sure to tell your doctor about all the medicines you take, especially medicines for asthma.

- Rarely, patients who use Twinject 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 during an injection. If you inject a young child with Twinject, 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.

Patients with certain medical conditions, or who take certain medicines, may get more side effects from Twinject, or the side effects may last longer. This includes patients who take certain types of medicines for asthma, allergies, depression, hyperthyroidism, high blood pressure, and heart disease. Patients with heart disease may feel chest pain (angina). Patients with mental disease or Parkinson's disease may have worsening symptoms of their illness. Twinject (epinephrine) can cause the following reactions. Some reactions can be serious. They usually go away with rest.

Common side effects of Twinject include:
• faster, irregular (wrong) or 'pounding' heartbeat
• throbbing headache
• paleness
• feelings of over excitement, anxiety, or fear
• weakness or shakiness
• dizziness
• nausea and vomiting
• sweating

These are not all the possible side effects of Twinject. For more information, ask your doctor or pharmacist.

How should I store Twinject?

The medicine in Twinject can be damaged by light. Therefore, keep it in the carrying case provided. Keep it at room temperature and protect it from freezing. Do not refrigerate.

Keep Twinject with you at all times.

Check your Twinject regularly to be sure:
• it has not expired
• the medicine in Twinject is not cloudy, discolored, or has particles in it.

Replace the Twinject if needed.

General information about the safe and effective use of Twinject.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Twinject for a condition for which it was not prescribed. Do not give Twinject to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Twinject. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Twinject that is written for health professionals.

Rx only.

Manufactured for and Distributed by: Amedra Pharmaceuticals LLC, Horsham, PA 19044

© 2014 Amedra Pharmaceuticals LLC, Horsham, PA. All rights reserved.

Revised May 2016

Twinject® auto-injector
(epinephrine injection, USP 1:1000)
Available as: 0.3 mg 0.15 mg

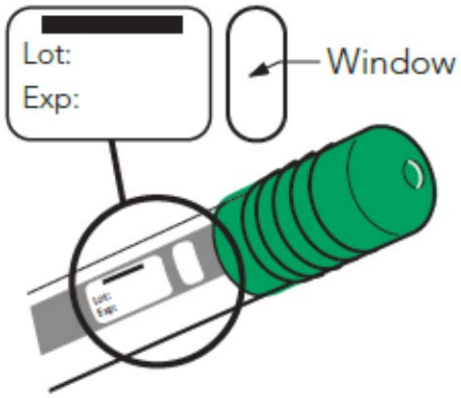
Patient Directions for Use

Before Use Make Sure Medicine Is Ready When You Need It

Look at the medicine in the Twinject regularly. If it looks cloudy, is discolored, has particles in it, or if the expiration date has passed, the Twinject should be replaced.

In the event of a life-threatening allergic reaction, you should go ahead and use an out-of-date or discolored product, if that is all you have.

Do NOT remove GREEN caps until you are ready to use the Twinject.



The following instructions should be followed for both Twinject 0.15mg and Twinject 0.3mg. Additional video instructions on the use of Twinject are available at www.xxxxx.xxx.

FIRST DOSE

STEP A

• Pull off **GREEN** end cap with the [**1**]; you will now see a **RED** tip. Never put thumb, finger, or hand over the **RED** tip.

• Pull off **GREEN** end cap with [**2**].

STEP B

• If you are administering Twinject 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 side of your thigh (upper leg) as shown. It can go through clothes.

• Press down hard until the needle enters your thigh (upper leg) through your skin. Hold it in place while slowly counting to 10.

• Remove the Twinject from your thigh.

• Check the **RED** tip, if the needle is exposed you received the dose. If needle is not visible, repeat First Dose step B.

• Immediately prepare for the second dose.

It is very important to monitor symptoms closely after the first dose is given, including watching for new symptoms. If new symptoms have appeared or symptoms have not improved within about 10 minutes, a second dose is needed.

SECOND DOSE

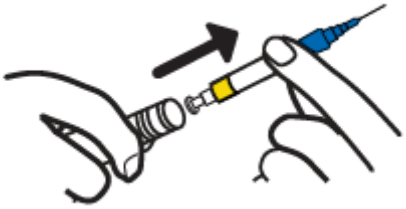
STEP A

• Unscrew and remove the **RED** tip.

Be careful of the exposed needle.

STEP B

• Grab the **BLUE** plastic to pull the syringe out of the barrel (do not touch the needle).



STEP C

• Slide the **YELLOW** collar off the plunger. Be careful not to pull up on the plunger while removing the **YELLOW** collar.

STEP D

• If your symptoms have not improved within about 10 minutes since the first injection, you need a second dose.

• If you are administering

Twinject to a young child, hold the leg firmly in place and limit movement prior to and while administering an injection.

• Put the needle into your thigh (upper leg), through your skin, as shown.

• Push the plunger down all the way until it cannot go any further.

• Remove the Twinject from your skin.

• Get emergency medical help right away.

• If a second dose is not needed and after professional medical attention is received, throw away the unused medicine as directed in the after use/disposal directions of this leaflet.

• After the first and second dose, liquid will remain in the syringe that can't be used.

Get emergency medical help right away. Call 911.

AFTER USE/DISPOSAL

• Put the syringe, needle first into the carrying case.

• Put the other half of the carrying case on and close it.

• Give your used Twinject to a healthcare worker for proper disposal. Do NOT throw away in a regular trash can.

For inquiries call X-XXX-XXXX-XXX

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

Revised May 2016

Manufactured for and Distributed by: Amedra Pharmaceuticals LLC, Horsham, PA 19044
© 2014 Amedra Pharmaceuticals LLC, Horsham, PA. All rights reserved.