

## Therapeutic Class Overview

### Epinephrine Products for Anaphylaxis

#### INTRODUCTION

- Anaphylaxis, a potentially fatal disorder, is a **severe**, acute, multisystem syndrome with rapid onset resulting from a sudden release of mast cell- and basophil-derived mediators into circulation. Most commonly, it results from immunologic reactions to foods, medications, and insect stings. In humans, the heart, vasculature system, and lungs are predominately affected during an anaphylactic reaction, and fatalities can result from circulatory collapse and respiratory arrest (American Heart Association, 2005; **Sicherer, 2017**).
- **Epinephrine can be life-saving when administered as rapidly as possible once anaphylaxis is recognized**, and is the treatment of choice because the benefits associated with epinephrine are greater than any other available pharmacologic intervention (e.g., antihistamines, bronchodilators, glucocorticoids). Epinephrine is the only agent that prevents and reverses airflow obstruction in the upper and lower respiratory tracts, as well as cardiovascular collapse. The therapeutic actions of epinephrine result from alpha-1 ( $\alpha_1$ ), beta-1 ( $\beta_1$ ), and beta-2 ( $\beta_2$ ) adrenergic receptor agonist effects and include increased vasoconstriction ( $\alpha_1$ ), increased peripheral vascular resistance ( $\alpha_1$ ), decreased mucosal edema ( $\alpha_1$ ), increased inotropy ( $\beta_1$ ), increased chronotropy ( $\beta_1$ ), increased bronchodilation ( $\beta_2$ ), and decreased release of mediators of inflammation from mast cells and basophils ( $\beta_2$ ) (Campbell et al, 2014; **Sicherer, 2017**).
- In general, pharmacologic treatment of anaphylaxis is based upon extrapolation from therapies utilized in cardiac arrest and asthma, uncontrolled clinical trials with humans who develop anaphylaxis during insect sting challenges, randomized controlled trials of interventions such as epinephrine in people not experiencing anaphylaxis at the time of administration, and animal anaphylaxis models. Randomized, placebo-controlled trials that meet current standards have not been performed for any pharmacologic intervention in humans experiencing anaphylaxis. Of note, placebo-controlled trials with epinephrine will never be performed, due to ethical considerations in a disorder that can kill within minutes and mandates prompt epinephrine administration.
- The epinephrine products for anaphylaxis (ADRENALCLICK<sup>®</sup>, AUVI-Q<sup>®</sup>, EPIPEN<sup>®</sup>, EPIPEN JR<sup>®</sup>, and authorized generics of ADRENALCLICK, EPIPEN, and EPIPEN JR) are all Food and Drug Administration (FDA) approved for the emergency treatment of severe allergic reactions. All agents are available as single use, auto-injectors to be administered as an intramuscular or subcutaneous injection into the anterolateral aspect of the thigh. Based on clinical trial data, intramuscular administration is preferred as it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine (American Heart Association, 2005; Simons et al, 2001; Simons et al, 1998).
- These agents are intended for immediate administration in patients with a history of anaphylactic reaction, and **prompt prehospital epinephrine injection is associated with a lower risk of hospitalization and fatality**. Furthermore, these agents are designed for emergency supportive therapy and are not intended to substitute immediate medical care. In conjunction with the administration of one of these agents, patients should seek appropriate medical care (**Sicherer, 2017**).
- Each agent is available as a 0.15 and 0.3 mg injection, and differences among the various agents are minimal and include specific packaging and administration requirements. Based on a comparison of package inserts, a notable difference between the products is that only ADRENALCLICK **and its' authorized generics'** needles are exposed after the injection. Furthermore, AUVI-Q is the first epinephrine auto-injector with audio instructions that directs patients and caregivers through the injection process. **AUVI-Q was voluntarily recalled in 2015 due to reports of device malfunctions, and was re-launched with manufacturing modifications in February 2017 (DRUGS@FDA, 2017; FDA recall press release, 2015; Kaléo Pharmaceuticals press release, 2016; Tirrell, 2017)**.
- Medispan class: Anaphylaxis Therapy Agent

**Table 1. Medications Included Within Class Review**

Drug	Manufacturer	FDA Approval Date	Generic Availability
ADRENALIN (epinephrine injection)†	Amreda Pharmaceuticals, Impax Generics	05/30/2003	✓†
AUVI-Q (epinephrine injection)‡	Kaléo Pharmaceuticals	08/10/2012	-
EPIPEN (epinephrine injection)	Mylan	12/22/1987	✓†
EPIPEN JR (epinephrine injection)			

\*ADRENALIN brand is currently not marketed.

† Authorized generics are available for all strengths. All generics are rated as “BX” and are not considered to be therapeutically equivalent by the FDA due to insufficient data.

‡ Kaléo Pharmaceuticals relaunched AUVI-Q in February 2017.

(Drugs@FDA, 2017; FDA Listing of Authorized Generics, 2017; Kaléo Pharmaceuticals press release, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

**INDICATIONS**

**Table 2. FDA-Approved Indications**

Indication	Epinephrine
Emergency treatment of severe allergic reactions (Type 1) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants), 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	✓

(Prescribing information: ADRENALIN, 2016; AUVI-Q, 2016; epinephrine, 2016; EPIPEN, 2016; EPIPEN JR, 2016)

**CLINICAL EFFICACY SUMMARY**

- A thorough literature search failed to retrieve any clinical trials evaluating the epinephrine products for anaphylaxis in their FDA-approved indications. It has been noted that controlled clinical trials evaluating epinephrine for this indication will never be performed, due to ethical considerations in a disease that can kill within minutes and mandates prompt epinephrine administration. As noted in the FDA-approved package labeling of the various agents, epinephrine is essential for the treatment of anaphylaxis.
- Epinephrine is the recognized treatment of choice for severe allergic reactions and anaphylaxis, as it is the only pharmacologic intervention that prevents and reverses obstruction to airflow in the upper and lower respiratory tracts (American Academy of Allergy, Asthma and Immunology [AAAAI] Board of Directors, 1998; Boyce et al, 2011; Fineman et al, 2015; Campbell et al, 2014; Golden et al, 2017; Kemp, 2008; Lieberman et al, 2015; National Institute of Allergy and Infectious Diseases, 2010; Sampson et al, 2014; Sicherer, 2017; Simons et al, 1998; Simons et al, 2001; Simons et al, 2011; Simons et al, 2012; Simons et al, 2013; Simons et al, 2015).
- It is recommended that patients who have a history of anaphylaxis or systemic reaction to allergens, including insect stings or foods, should be given a prescription for an injectable epinephrine device and be advised to carry it with them at all times (Boyce et al, 2011; Golden et al, 2017; Sampson et al, 2014).

## SAFETY SUMMARY

- There are no absolute contraindications to the use of the epinephrine products for anaphylaxis in a life-threatening allergic reaction.
- 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 administered.
- Epinephrine should be administered with caution to patients with cardiac arrhythmias, coronary artery or organic heart disease or hypertension, or in patients who are on medications that may sensitize the heart to arrhythmias. In patients with coronary insufficiency or ischemic heart disease, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. The presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.
- 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. To decrease the risk of Clostridium infection, do not inject the drug into the buttock. Should signs and symptoms of infection occur, patients should seek medical care.
- Epinephrine is not intended as a substitute for immediate medical care; in conjunction with its administration, patients should seek appropriate medical care. More than two sequential doses of epinephrine should only be administered under direct medical supervision.
- Epinephrine should only be injected into the anterolateral aspect of the thigh. In children, the leg should be held firmly in place prior to and during injection to reduce injury, as lacerations, bent needles, embedded needles, and other injuries have been observed after epinephrine auto-injector administration on children. Avoid accidental injection into the hands or feet as this may result in loss of blood flow to the area. Furthermore, epinephrine should not be injected into the buttock. If an accidental injection occurs, patients should inform a health care provider when he/she goes to the nearest emergency room for further treatment of anaphylaxis.
  - An analysis evaluated 22 cases of epinephrine auto-injector-related injuries including lacerations and embedded needles in children. In response, product warnings were updated to require immobilization of a child's leg prior to and during injection, and injection time for the EPIPEN and EPIPEN JR was reduced from 10 to 3 seconds (Brown et al, 2016).
- Possible inadvertent intravascular administration should also be avoided.
- Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations. Epinephrine auto-injectors, ADRENALICK, and AUVI-Q contain sodium bisulfite; whereas, EPIPEN and EPIPEN JR contain sodium metabisulfite. Thus, all forms of epinephrine used for anaphylaxis contain sulfites that may cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. Because the alternatives to epinephrine in a life-threatening situation may not be satisfactory, the presence of a sulfite should not deter administration of the agent for the treatment of serious allergic or other emergency situations, even in a sulfite-sensitive patient.
- 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. 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.
- Several drug-drug interactions exist with epinephrine. 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, levothyroxine sodium, and certain antihistamines. The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs. The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs. Ergot alkaloids may also reverse the pressor effects of epinephrine.

## DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Dose	Administration Considerations
Epinephrine*	<p>Injection: 0.15 mg/0.15 mL (AUVI-Q, epinephrine)</p> <p>0.15 mg/0.3 mL (epinephrine, EPIPEN JR)</p> <p>0.3 mg/0.3 mL (AUVI-Q, epinephrine, EPIPEN)</p>	<p>Emergency treatment of severe allergic reactions (Type 1) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants), 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:</p> <p>Injection: 0.15 mg (15 to 30 kg) or 0.3 mg (<math>\geq 30</math> kg)</p>	<p>Self-administered auto-injectors that deliver a single dose of either strength.</p> <p>Injection should be administered into the anterolateral aspect of the thigh, through clothing if necessary.</p> <p>Administration time varies by device (i.e., 5 seconds for AUVI-Q; 3 seconds for EPIPEN, EPIPEN JR, and authorized generic; and 10 seconds for ADRENACLICK authorized generic).</p> <p>In conjunction with its administration, patients should seek appropriate medical care.</p> <p>Any remaining volume that is left after administration cannot be further administered and should be discarded with the device.</p> <p>More than two sequential doses of epinephrine should only be administered under direct medical supervision.</p>

Note: All productions only available in a two pack containing two auto-injectors.

\*ADRENACLICK brand currently not marketed.

## SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Epinephrine	No dosage adjustment required in the elderly.	No dosage adjustment required in children.*	No dosage adjustment required.	No dosage adjustment required.	<p>Pregnancy Category C**</p> <p>Unknown whether excreted in breast milk; use with caution.</p>

\*Since the doses of epinephrine delivered from the various agents within this class are fixed, physicians should consider other forms of injectable epinephrine if doses lower than those available from these agents are felt to be necessary.

\*\* Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

## CONCLUSION

- Anaphylaxis, a potentially fatal disorder, is an acute, multisystem syndrome resulting from a sudden release of mast cell- and basophil-derived mediators into the circulation.
- Foods, medications, and insect stings that cause a subsequent immunologic reaction are the most common reason for an anaphylactic reaction to occur. In humans, the heart, vasculature system and lungs are predominantly affected during anaphylaxis, and fatalities can result from circulatory collapse and respiratory arrest. Guidelines recommend prompt epinephrine injection for sudden onset of any anaphylaxis symptoms after exposure to an allergen that previously caused anaphylaxis in a patient (American Heart Association, 2005; Sicherer, 2017).
- **Epinephrine can be life-saving when administered as rapidly as possible once anaphylaxis is recognized**, and is the only pharmacologic intervention that prevents and reverses obstruction to airflow in the upper and lower respiratory tracts (AAAAI Board of Directors, 1998; Boyce et al, 2011; Campbell et al, 2014; Fineman et al, 2015; Golden et al, 2017; Kemp et al, 2008; Lieberman et al, 2015; National Institute of Allergy and Infectious Diseases, 2010; Sampson et al, 2014; Sicherer, 2017; Simons et al, 1998; Simons et al, 2001; Simons et al, 2011; Simons et al, 2012; Simons et al, 2013; Simons et al, 2015).
- Acting as an agonist at  $\alpha_1$ ,  $\beta_1$  and  $\beta_2$  adrenergic receptors, epinephrine works in the emergency treatment of anaphylaxis by causing increased vasoconstriction ( $\alpha_1$ ), increased peripheral vascular resistance ( $\alpha_1$ ), decreased mucosal edema ( $\alpha_1$ ), increased inotropy ( $\beta_1$ ), increased chronotropy ( $\beta_1$ ), increased bronchodilation ( $\beta_2$ ) and decreased release of mediators of inflammation from mast cells and basophils ( $\beta_2$ ). Of note, clinical trials evaluating epinephrine for emergency anaphylaxis treatment will never be performed, due to ethical considerations in a disorder that can kill within minutes and mandates prompt epinephrine administration (Song et al, 2014).
- Included in this review are the epinephrine products for anaphylaxis which are all FDA-approved for the emergency treatment of severe allergic reactions. As noted in their FDA-approved package labeling, epinephrine is essential for the treatment of anaphylaxis, and these agents are designed for emergency supportive therapy. They are not intended to substitute immediate medical care; in conjunction with the administration of one of these agents, patients should seek appropriate medical care.
- All of the epinephrine products for anaphylaxis are available as single use, auto-injectors to be administered, by the patient or caregiver, as an intramuscular or subcutaneous injection into the anterolateral aspect of the thigh.
- Differences among the various epinephrine agents are minimal and include specific packaging and administration requirements. AUVI-Q is the only epinephrine auto-injector that contains audio instructions to guide patients and caregivers through the injection process. Each agent is available as a 0.15 and 0.3 mg injection, and **authorized** generics are available within the class.

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