

## 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 predominantly affected during an anaphylactic reaction, and fatalities can result from circulatory collapse and respiratory arrest. Symptoms consist of progressive swelling, breathing difficulty, and itchy rash, leading to shock and potentially death (*Singletary et al 2015, Sicherer et al 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 et al 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 include Adrenaclick, Auvi-Q, EpiPen, EpiPen Jr, and Symjepi, with authorized generics available for Adrenaclick, EpiPen, and EpiPen Jr. **An AB-rated (therapeutically equivalent) generic for EpiPen and EpiPen Jr was recently approved by the Food and Drug Administration (FDA), but has not yet launched in the marketplace** (*Orange Book: Approved drug products with therapeutic equivalence evaluations 2018*). These epinephrine products are all FDA-approved for the emergency treatment of severe allergic reactions. All agents are available 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 (*Sicherer et al 2017, Simons et al 1998, Simons et al 2001*).
- Differences among the various agents include specific packaging and administration requirements. Each agent is available as a 0.15 and/or 0.3 mg injection, except Symjepi, which is only available as a 0.3 mg injection, and Auvi-Q, which is also available as a 0.1 mg injection. Symjepi is only available as a prefilled syringe that requires manual insertion of the needle into the thigh, while all other agents are available as auto-injectors. In addition, Symjepi, Adrenaclick, and Adrenaclick's authorized generics' needles are exposed after the injection. Auvi-Q has the unique characteristic of being the first epinephrine auto-injector with audio instructions that instructs patients and caregivers through the injection process.
- 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 et al 2017*).
- Medispan class: Anaphylaxis therapy agents.

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

Drug	Generic Availability
Adrenaclick (epinephrine injection)*	-†
Auvi-Q (epinephrine injection)	-
EpiPen (epinephrine injection)	-†‡
EpiPen Jr (epinephrine injection)	
Symjepi (epinephrine injection)	-

\*Adrenaclick brand is currently not marketed.

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

‡ An AB-rated generic has been approved by the FDA on 8/16/18, but launch is currently pending. Generics given an “AB” rating by the FDA are considered to be therapeutically equivalent to the reference drug.

(Drugs@FDA 2018, FDA listing of authorized generics 2018, Orange Book: Approved drug products with therapeutic equivalence evaluations 2018)

## INDICATIONS

**Table 2. Food and Drug Administration 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: Adrenaclick 2016, Auvi-Q 2017, EpiPen 2018, EpiPen Jr 2018, Symjepi 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## 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.
- Epinephrine is essential for the treatment of anaphylaxis as it is the only pharmacologic intervention that prevents and reverses obstruction to airflow in the upper and lower respiratory tracts. Immediate pre-hospital administration of epinephrine is associated with a lower risk of hospitalization and death in patients with anaphylaxis (Bock et al 2001, Bock et al 2007, Boyce et al 2010, Campbell et al 2014, Fineman et al 2015, Fleming et al 2015, Golden et al 2017, Kemp et al 2008, Lieberman et al 2015, Sampson et al 1992, Sampson et al 2014, Sicherer et al 2017, Simons et al 1998, Simons et al 2001).
- A randomized crossover study in healthy adults revealed that Auvi-Q and EpiPen were bioequivalent and had similar peak, total epinephrine exposure, and safety profiles after a single injection of 0.3 mg (Edwards et al 2013).

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#### CLINICAL GUIDELINES

- Current clinical guidelines including those from the American Academy of Pediatrics, the World Allergy Organization, and the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology consistently recommend epinephrine as the first-line medication of choice for the treatment of anaphylaxis due to its life-saving effects. It is suggested that patients who have a history of anaphylaxis or systemic reaction to allergens, including insect stings or foods, be prescribed an injectable epinephrine agent and be advised to carry it with them at all times. Consideration may also be given to patients who do not have a history of anaphylaxis but are at high risk of an anaphylactic reaction (*Boyce et al 2010, Campbell et al 2014, Golden et al 2017, Kemp et al 2008, Lieberman et al 2015, Sampson et al 2014, Sicherer et al 2017, Simons et al 2015*).
- The guidelines state that auto-injectors are preferred over prefilled syringes in the community setting due to ease of use and accuracy of dosing, but do not differentiate between the individual auto-injector products. Choice of an epinephrine agent should be evaluated on an individual patient basis; some factors to consider are size, ease of use, ease of carrying, needle protection, and cost.
- Antihistamines, glucocorticoids, and bronchodilators may be used as adjunct therapy to epinephrine, but should not be used as initial or sole therapy as these agents do not have any life-saving properties (*Lieberman et al 2015, Sicherer et al 2017, Simons et al 2015*).

#### 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 2 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. 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, AdrenaClick, and Auvi-Q contain sodium bisulfite; whereas, EpiPen, EpiPen Jr, and Symjepi contain sodium metabisulfite. Thus, all forms of epinephrine used for anaphylaxis contain sulfites that may cause allergic-type reactions

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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.
- There are no adequate or well-controlled studies of the acute effect of epinephrine in pregnant women. Although animal reproductive studies have shown an adverse effect on the fetus, epinephrine is still considered the first-line medication of choice for anaphylaxis during pregnancy due to its life-saving effects.

## DOSING AND ADMINISTRATION

**Table 3. Dosing and Administration**

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Epinephrine	Auto-injectors (Adrenaclick, Auvi-Q, EpiPen, EpiPen Jr)  Prefilled syringe (Symjepi)	Intramuscular or subcutaneous injection	Inject 1 dose; an additional dose may be needed with severe persistent anaphylaxis.  More than 2 sequential doses of epinephrine should only be administered under direct medical supervision.	Dosing is based on weight: <ul style="list-style-type: none"> <li>• Patients 7.5 to 15 kg: 0.1 mg</li> <li>• Patients 15 to 30 kg: 0.15 mg</li> <li>• Patients <math>\geq</math> 30 kg: 0.3 mg</li> </ul> <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.</p> <p>Injection should be administered into the anterolateral aspect of the thigh, through clothing if necessary; do not administer repeated injections at the same site.</p> <p>As a prefilled syringe, Symjepi requires the patient or caregiver to</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				manually inject the needle into the skin.

See the current prescribing information for full details

## 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. Current clinical guidelines recommend prompt epinephrine injection for sudden onset of any anaphylaxis symptoms after exposure to an allergen that previously caused anaphylaxis in a patient.
- 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 (*Boyce et al 2010, Campbell et al 2014, Fineman et al 2015, Golden et al 2017, Kemp et al 2008, Lieberman et al 2015, Sampson et al 2014, Sicherer et al 2017, Simons et al 1998, Simons et al 2001, 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*).
- Adrenaclick, Auvi-Q, EpiPen, EpiPen Jr, and Symjepi 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 these epinephrine products for anaphylaxis are available as single use injections to be administered, by the patient or caregiver, as an intramuscular or subcutaneous injection into the anterolateral aspect of the thigh. Intramuscular administration is preferred as it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine.
- Differences among the various epinephrine agents include specific packaging and administration requirements. Adrenaclick, Auvi-Q, EpiPen, and EpiPen Jr are available as auto-injectors, while Symjepi is only available as a prefilled syringe that requires manual insertion of the needle into the thigh. Each agent is available as a 0.15 and 0.3 mg injection, except Symjepi, which is only available as a 0.3 mg injection, and Auvi-Q, which is also available as a 0.1 mg injection. Auvi-Q is the only epinephrine agent that contains audio instructions to guide patients and caregivers through the injection process.

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