Epinephrine, Self-Injected Agents
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Trade Name	Manufacturer	FDA-Approved Indications
epinephrine 0.3 mg	No trade name[1] Auvi-Q®[2] Epipen®[3] Symjepi™[4]	generic* Kaléo generic, Mylan Specialty† Adamis‡	▪ Emergency treatment of Type I allergic reactions including anaphylaxis to stinging insects, biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances, and other allergens ▪ Emergency treatment of idiopathic anaphylaxis ▪ Emergency treatment of exercise-induced anaphylaxis
epinephrine 0.15 mg	No trade name[5] Auvi-Q[6] Epipen Jr®[7] Symjepi[8]	generic* Kaléo generic, Mylan Specialty† Adamis‡	
epinephrine 0.1 mg	Auvi-Q[9]	Kaléo	

* The generic epinephrine by Impax/Amneal is an authorized generic of Amedra's/Impax's Adrenaclick®. Brand Adrenaclick by Impax/Shionogi is no longer manufactured. The generic epinephrine by Impax/Amneal is not interchangeable for other available products in this class.

† The generic epinephrine products by Mylan Specialty are authorized generics of Epipen and Epipen Jr. A generic epinephrine by Teva was approved under an abbreviated new drug application (ANDA) as an AB-rated generic version of Epipen 0.3 mg and Epipen Jr 0.15 mg.

‡ Symjepi, an epinephrine prefilled syringe, is administered by manual injection.

OVERVIEW

Anaphylaxis is an acute, life-threatening medical emergency with many potential triggers. According to the 2015 anaphylaxis practice parameter, anaphylaxis is currently defined as 1 of 3 scenarios based on the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) criteria:

- The acute onset of a reaction (minutes to several hours) with involvement of the skin, mucosal tissue, respiratory tract, and/or reduced blood pressure
- Rapid onset of a reactions after exposure to a likely allergen that involved 2 organ systems, including the skin/mucosal tissue, respiratory tract, reduced blood pressure, and/or persistent gastrointestinal symptoms
- Reduced blood pressure after exposure to a known allergen.[10]

Anaphylaxis may be fatal and requires prompt recognition and immediate management.[11] Anaphylaxis has a rapid onset with multiple organ-system involvement and is primarily seen in sensitized individuals after exposure to specific antigens. Reactions typically follow a uniphasic pattern; however, biphasic anaphylaxis, in which recurrent anaphylaxis occurs 1 to 78 hours following resolution of the initial episode, can occur.[12] Biphasic anaphylaxis is estimated to occur in about < 1% to 20% of patients. Severe anaphylaxis or the need for > 1 dose of epinephrine are risk factors for biphasic reactions. According to the 2010 NIAID-Sponsored Food Allergy Guidelines, intramuscular (IM) epinephrine is the treatment of choice for all instances of anaphylaxis resulting from food or any other cause.[13] The American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) advise that patients with a history of an anaphylactic reaction and those at an increased risk of anaphylaxis should receive a prescription for an epinephrine auto-injector; epinephrine prefilled syringe (Symjepi) was not available at the time most of these guidelines were published.[14,15,16,17] Epinephrine

should be administered immediately at first signs or symptoms of anaphylaxis. Although epinephrine has a rapid onset of action, it is also quickly metabolized. Therefore, repeat dosing may be necessary if anaphylactic symptoms do not fully resolve in 5 to 15 minutes. Patients should carry 2 doses of epinephrine. More than 2 sequential doses of epinephrine should only be administered under direct medical supervision. Protracted anaphylaxis may persist beyond 24 hours. Concurrent beta-blocker therapy may adversely affect the response to management. Secondary measures include circulatory support, antihistamines (both H_1 and H_2 antagonists), corticosteroids, and, occasionally, bronchodilators. Careful post-treatment observation of patients who suffer an anaphylactic episode is necessary with ready access to emergency care for the following 48 hours. Patients who experience hypotension should remain recumbent until hemodynamically stable or asymptomatic, due to an increased risk of sudden death upon sitting upright prematurely.[18]

Anaphylaxis may occur as a result of exposure to specific agents (e.g., food, medication, insect bites/stings).[19] Patients should be educated about specific exposures that may place them at risk for future reactions. They should also be provided counseling on avoidance measures to reduce risk for such exposures. Patients who have experienced anaphylaxis should carry self-injectable epinephrine for emergency use. These patients should also carry identification indicating they are prone to anaphylaxis and indicate the responsible agent.

In 2017, the American Academy of Pediatrics (AAP) updated their guidance on the use of epinephrine for first-aid management of anaphylaxis.[20] They recommend that at-risk patients should be prescribed an epinephrine auto-injector for first-line treatment of anaphylaxis, particularly in patients with asthma. They describe at-risk patients as those with a history of anaphylactic reactions, idiopathic anaphylaxis, and with an increased risk of anaphylaxis, such as those with known food sensitivities (regardless of no prior anaphylaxis) and including patients living in remote areas with limited access to emergency medical services. Use of epinephrine as soon as anaphylaxis is recognized is associated with a lower risk of hospitalization and death. AAP indicates that the 0.15 mg dose is high for pediatrics weighing ≤ 7.5 kg (e.g., infants), and many physicians may prefer the 0.15 auto-injector over the caregiver drawing up a lower dose as this poses the risk of delayed and/or incorrect dosing. The epinephrine 0.1 mg auto-injector (Auvi-Q) was not available at the time the updated guidelines were developed.

PHARMACOLOGY[21]

Epinephrine acts on both alpha- and beta-adrenergic receptors. By acting on the alpha-adrenergic receptors, epinephrine reduces vasodilation and increases vascular permeability that occurs during anaphylaxis which alleviates loss of intravascular fluid volume and hypotension. Through its action on beta-adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation which alleviates bronchospasm, wheezing, and dyspnea that may occur during anaphylaxis. Epinephrine may also be useful in reducing urticaria, pruritus, angioedema, and gastrointestinal/genitourinary symptoms associated with anaphylaxis as a result of its relaxing effects on the smooth muscle of the stomach, intestines, uterus, and urinary bladder.

PHARMACOKINETICS[22]

Drug	Route of Administration	Onset of Action	Duration of Action
epinephrine (Auvi-Q, Epipen, Epipen Jr, Symjepi, generic)	SC	5 to 15 minutes	1 to 4 hours
	IM	Variable	1 to 4 hours

IM = intramuscular; SC = subcutaneous

CONTRAINDICATIONS/WARNINGS[23,24,25,26]

There are no absolute contraindications for the use of epinephrine in life-threatening situations; however, patients with cardiovascular disease, hyperthyroidism, diabetes, elderly individuals, pregnant women, and patients with Parkinson's disease are more prone to adverse effects when using self-injectable epinephrine. In cardiovascular disease, epinephrine may precipitate or aggravate angina pectoris, in addition to causing ventricular arrhythmias. Thus, epinephrine should be administered with caution in such patients. Generic epinephrine, Auvi-Q, Epipen, Epipen Jr, and Symjepi contain sulfites. The presence of a sulfite in these products should not deter administration of the drug for treatment of serious allergic or other emergency situations, even if the patient is sulfite-sensitive.

Accidental injection into fingers, hands, or feet should be avoided. Injecting the medication into one of these locations could cause vasoconstriction resulting in a loss of blood flow and hypothermia in the affected area that may require medical attention. Epinephrine should not be injected into the buttocks, which may not provide effective treatment of anaphylaxis. Epinephrine must not be injected intravenously. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to a rapid rise in blood pressure.

Cases of serious skin and soft tissue infection, including necrotizing fasciitis and myonecrosis, at the injection site have rarely been reported.

Upon administration, hold thigh firmly to prevent lacerations, bent needles, and embedded needles, as reports have been made in young children or infants who were moving during injection.

Immediate medical care should be sought in conjunction with epinephrine administration.

In March 2020, the United States (US) Food and Drug Administration (FDA) issued an alert regarding the potential for delayed injection or prevention of proper injection for Epipen, Epipen Jr, and their authorized generics.27 Issues with injection may arise due to due to (1) device failure due to spontaneous activation from sideways force removing blue safety release; (2) device failure from inadvertent/spontaneous activation due to a raised blue safety release; (3) difficulty removing device from carrier tube; and (4) user error. Subsequently, updated patient information and instructions for use were added to the package inserts of these products. The communication was not a device recall.

In June 2020, the FDA issued an alert regarding inspection of select lots of Impax/Amneal's epinephrine 0.3 mg autoinjector to ensure the presence of the yellow "stop collar."28 This component helps to ensure the device provides the proper dose; if the component is missing, it is possible the device could deliver a double dose to a patient. The FDA and Impax provided guidance on how to assess for the presence of the component. The communication was not a device recall.

DRUG INTERACTIONS[29,30,31,32,33]

Epinephrine should be used cautiously in patients receiving any of the following drugs due to the increased risk of adverse effects, including cardiac arrhythmias: albuterol, dobutamine, dopamine, isoproterenol, metaproterenol, norepinephrine, phenylephrine, phenylpropanolamine, pseudoephedrine, ritodrine, salmeterol, and terbutaline. Certain types of antidepressants, such as tricyclic antidepressants and monoamine oxidase inhibitors, along with thyroid hormone replacement and certain antihistamines, particularly chlorpheniramine, tripelennamine, and diphenhydramine, may also potentiate epinephrine physiological effects. Likewise, beta-adrenergic blocking drugs, such as propranolol, may antagonize the cardio stimulating and bronchodilating effects of epinephrine. Alpha-adrenergic blocking drugs, such as phentolamine, may antagonize vasoconstricting and hypertensive effects of epinephrine. Ergot alkaloids may also reverse the vasoconstricting effects of epinephrine. Patients taking cardiac glycosides, diuretics, or anti-arrhythmics while receiving epinephrine should be observed carefully for the presence of cardiac arrhythmias.

ADVERSE EFFECTS[34,35,36,37,38]

Adverse reactions to epinephrine may include transient central nervous system (CNS) symptoms, such as anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, and/or headache. Other adverse effects may include sweating, palpitations, pallor, nausea/vomiting, and/or respiratory difficulties. These effects usually subside quickly, with rest and recumbent position. Although these reactions may occur in patients receiving therapeutic doses, they are more likely to occur in patients with hypertension or hyperthyroidism. Cardiovascular adverse effects, such as arrhythmias and rapid rises in blood pressure, have been observed in patients receiving epinephrine products. Arrhythmias, including as fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or utilizing certain drugs. Furthermore, rapid increases in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with underlying heart disease. Angina may develop and/or worsen in patients with coronary artery disease. Rare cases of stress cardiomyopathy have been reported. Accidental injection into the fingers, hands, or feet may result in loss of blood flow to the affected area. There are a number of adverse events that may be experienced as a result of accidental injections, such as 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. It should be noted that, in an acute life-threatening allergic reaction, the potential for epinephrine to produce the types of adverse reactions stated above, does not contraindicate its use.

SPECIAL POPULATIONS[39,40,41,42]

Geriatrics

Elderly patients are more prone to adverse effects when using epinephrine and should therefore use self-injectable epinephrine with caution. This is especially true for geriatric patients with underlying cardiovascular and/or metabolic disease.

Pediatrics

The self-injectable epinephrine products in this category are approved for use in children based on body weight. Please consult the individual package inserts for specific product information. It is unknown if epinephrine 0.1 mg (Auvi-Q) is safe and effective in children weighing < 7.5 kg.

Pregnancy

Labeling for Auvi-Q, Epipen, Epipen Jr, and Symjepi complies with the Pregnancy and Lactation Labeling Rule (PLLR). The labeling for these products state that there are no adequate and well-controlled studies of the acute effect of epinephrine in pregnant women; however, epinephrine is the first-line medication of choice for the treatment of anaphylaxis, including in pregnant women.

Renal Impairment

There are no specific recommendations for dosage adjustments necessary for patients with impaired renal function. Please consult the individual package inserts for specific product information.

Hepatic Impairment

There are no specific recommendations for dosage adjustments necessary for patients with impaired hepatic function. Please consult the individual package inserts for specific product information.

DOSAGES[43,44,45,46]

Drug	Patient Weight			Availability **Special Note:** Inject IM or SC in the anterolateral aspect of the thigh, through clothing if necessary. Time to maximum serum concentration (Cmax) is shortest when administered IM to the lateral aspect of the thigh.[47]
	≥ 30 kg (≥ 66 lbs)	15 kg to 30 kg (33 to 66 lbs)	7.5 kg to 15 kg (16.5 to 33 lbs)	
epinephrine (Auvi-Q, Epipen, Epipen Jr, Symjepi)	0.3 mg injection	0.15 mg injection	0.1 mg injection (Auvi-Q only)	**Generics of Adrenaclick:** 0.15 mg/0.15 mL, 0.3 mg/0.3mL auto-injector ▪ Each strength packaged with 2 auto-injectors; training devices for the generic are available to order ▪ Each device is intended for a single administration, remaining volume should be discarded; > 2 subsequent doses should be administered under direct medical supervision **Auvi-Q**: 0.1 mg/0.1 mL, 0.15 mg/0.15 mL, 0.3 mg/0.3 mL auto-injector ▪ Auvi-Q 0.1 mg, Auvi-Q 0.15 mg, and Auvi-Q 0.3 mg are available with 2 auto-injectors and a single Auvi-Q trainer device ▪ Each device is intended for a single administration, although the trainer device may be used multiple times; repeat injections may be necessary with an additional Auvi-Q; however, more than 2 subsequent doses should be administered under direct medical supervision **Epipen and generic equivalents:** 0.3 mg/0.3 mL auto-injector **Epipen Jr and generic equivalents:** 0.15 mg/0.3 mL auto-injector ▪ Dual packs of both Epipen and Epipen Jr (Epipen 2-Pak and Epipen Jr 2-Pak) are available with 2 auto-injectors and 1 auto-injector trainer device ▪ Each device is intended for a single administration, remaining volume should be discarded; > 2 subsequent doses should be administered under direct medical supervision **Symjepi:** 0.15 mg/0.3 mL, 0.3 mg/0.3 mL prefilled syringe (PFS) ▪ Symjepi is available as a 2-pack containing 2 PFS ▪ Symjepi is administered via *manual* IM or SC injection; after the needle is in the thigh, the user should push the plunger down all the way until it clicks, then hold for 2 seconds before removing the needle from the leg

DEVICES[48,49,50,51]

These products are intended for immediate self-administration as emergency supportive therapy only and are not a substitute for immediate medical care.

Epinephrine injection auto-injectors and prefilled syringes (PFS) each contain 1.1 mL of epinephrine solution, delivering either 0.15 mg (0.15 mL) or 0.3 mg (0.3 mL) of epinephrine in a single administration. The remaining volume should be discarded.

Each strength of Auvi-Q contains 0.76 mL epinephrine solution. When activated, 0.3 mL, 0.15 mL, or 0.1 mg epinephrine solution is dispensed, for Auvi-Q 0.3 mg, Auvi-Q 0.15 mg, and Auvi-Q 0.1 mg, respectively. Any remaining solution should be discarded.

Epipen and Epipen Jr auto-injectors each contain 2 mL of epinephrine solution. Approximately 1.7 mL remains unusable after activation. Each Epipen delivers 0.3 mg (0.3 mL) epinephrine in a single dose. Each Epipen Jr delivers 0.15 mg (0.3 mL) epinephrine in a single dose.

The Symjepi PFS contains 0.8 mL of either 0.15 mg or 0.3 mg per 0.3 mL epinephrine solution. The syringe is overfilled for stability purposes; more than half of the solution remains in the syringe after use which cannot be reused.

Epipen, Epipen Jr, and epinephrine auto-injectors contain visual instructions on the devices. Auvi-Q devices include visible cues through light-emitting diode (LED) lights, audible beeps, and electronic voice instructions for use. For Symjepi, the user must manually inject the needle and push down the plunger. Once the plunger has been pushed all the way down, the user will hear a click and the solution window will be at least partially blocked, indicating that the correct dose has been injected.

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no comparative trials currently available for the self-injectable epinephrine products.

SUMMARY

Anaphylaxis is a life-threatening allergic reaction that can be caused by a variety of allergens including food, medications, insect stings and bites, and latex. All patients at risk of anaphylaxis are urged to carry self-injectable epinephrine (Auvi-Q, Epipen, Epipen Jr, Symjepi, or generic formulations). Strengths

include 0.3 mg for patients weighing ≥ 30 kg, 0.15 mg for patients 15 kg to 30 kg, and 0.1 mg for patients 7.5 mg to 15 kg. Currently, the only formulation available as 0.1 mg is the Auvi-Q auto-injector. Patients should be well informed by their physician and/or pharmacist of when to use this life saving medication.

Each of the self-injectable epinephrine devices allows patients to deliver a single dose from the unit via auto-injection. Unlike epinephrine auto-injectors, Symjepi is available as a prefilled syringe (PFS) that requires manual injection. The Auvi-Q device guides patients and caregivers through the injection process with audio and visual cues. The auto-injector formulations (Auvi-Q, Epipen, Epipen Jr, generics) are available as twin-packs containing 2 devices of either 0.3 mg or 0.15 mg, and the Symjepi PFS also is available as either 0.15 mg or 0.3 mg in twin-packs containing 2 syringes. While all the epinephrine self-injectors contain epinephrine, due to device differences they are not considered interchangeable, with the exception of Teva's generic epinephrine which is AB-rated to Epipen and Epipen Jr. Practice guidelines do not distinguish preference of one self-injectable epinephrine product over another.

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