



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Epinephrine Injection Devices
-January 2020-



Background:

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed epinephrine injection devices (i.e., auto-injectors, pre-filled syringes) at the January 2020 Winter meeting. Epinephrine is not currently named to the National Core Formulary nor has it been reviewed by the NPTC in the past. After evaluating current treatment guidelines, applicable research, and procurement data, the NPTC voted to **ADD epinephrine injection devices (both 0.15 mg and 0.3 mg dosages)** to the National Core Formulary. Epinephrine auto-injectors are preferred over pre-filled syringes. However, the episodic shortage of epinephrine products necessitates a diversity of options among epinephrine delivery devices.

Discussion:

In the United States, the lifetime risk of anaphylaxis is estimated at 1.6%. Admission rates for anaphylactic reactions have been on the rise over the last 2 decades and account for approximately 200 deaths per year¹. Foods are the largest trigger of anaphylaxis in children (85%) while medications are the greatest cause in adults (35%), followed by foods (32%), and insect venom (19%)².

Outpatient administration of epinephrine via auto-injection has been the mainstay of anaphylaxis treatment for over 30 years. Because epinephrine was the first synthesized hormone and has been in medical use for over 100 years, the recommended dosing and route has been determined largely through empiric means. Cochrane reviews on the use of epinephrine in anaphylaxis (2008) and epinephrine auto-injectors (2012) revealed no adequate trials to determine optimal route, dosing or auto-injection device^{3,4}.

The Food and Drug Administration has approved epinephrine for use with anaphylaxis at a dose of 0.01 mg/kg with a maximum single dose of 0.3 mg in pediatrics and 0.5 mg in adults. Three strengths of epinephrine auto-injectors are currently available in the United States, approved by weight ranges as follows: 0.1 mg (7.5-15 kg), 0.15 mg (15-30 kg), and 0.3 mg (over 30 kg). Use of these products in individuals at the upper and lower ends of these weight ranges results in doses at 50-133% of the 0.01 mg/kg goal, however optimal dosing has not been determined in adequate clinical trials⁵.

Currently, four brands of epinephrine auto-injectors (AdrenaClick[®], Auvi-Q[®], EpiPen[®], epinephrine USP auto-injector, generic) and one epinephrine pre-filled syringe (Symjepi[®]) are commercially available. Each epinephrine device has unique and important differing characteristics regarding their delivery including needle retraction, the provision of a trainer syringe, and varying hold times (on skin after injection). All devices are available in both the 0.15 mg and 0.3 mg strengths; at present only the Auvi-Q[®] auto-injector offers the 0.1 mg dose. Providers, patients and family members should be well-educated on the proper use and delivery technique for the prescribed device.

The use of epinephrine by auto-injection is recommended in all reviewed guidelines⁶⁻¹⁰. Failure to use epinephrine early in an anaphylactic event increases the risk of mortality, thus, the use of a written anaphylaxis action plan to assist in the early recognition and treatment of anaphylaxis is advised. Since the signs of anaphylaxis can be more difficult to identify in infants, an anaphylaxis action plan specific for infants should be used in this age group¹⁰. There is consensus that referral to an allergist after an initial anaphylaxis event is important for trigger confirmation, education on allergen avoidance and consideration of desensitization therapy, particularly in the case of insect (hymenoptera) venom, which is successful in preventing future events by 80-98%⁶.

All guidelines addressing pediatric use of epinephrine injection devices suggest alternate weight ranges for currently available products. The 0.15 mg epinephrine injection device, though approved down to 15 kg, is recommended for use down to 7.5 kg in most guidelines⁷⁻¹⁰. The one guideline published since the 0.1 mg epinephrine auto-injector became available advises that either the 0.1 mg or 0.15 mg product is appropriate for infants weighing 7.5-15 kg¹⁰. All guidelines recommend switching to the 0.3 mg epinephrine injection device at either 20 kg^{8,10} or 25 kg^{7,9} rather than the approved 30 kg threshold.

Intramuscular injection of epinephrine in the lateral thigh is the recommended route of administration. Subcutaneous administration can result in increased time to reach maximal plasma concentration while interosseous/periosteal injection can cause rapid absorption, similar to intravenous administration, which increases the risk of arrhythmia. The needle lengths of epinephrine auto-injectors could lead to subcutaneous injection in heavier individuals and interosseous injection in lean people. One study estimated, based on ultrasound-measured skin-to-muscle and skin-to-bone distances, that the risk for subcutaneous injection in children weighing between 7.5-15 kg was 69%, and in those between 15-30 kg, was 54% when using a 0.1 mg epinephrine auto-injector (7.4 mm needle). There was no risk of subcutaneous injection in either group using a 0.15 mg epinephrine auto-injector (13 mm needle). In these same weight ranges, the risk for interosseous/periosteal injection was 32% and 10% respectively, when using a 0.15 mg epinephrine auto-injector. No risk of interosseous/periosteal injection was identified with use of the 0.1 mg epinephrine auto-injector¹¹. In interpreting this data, it is important to keep in mind the limitations of ultrasound in accurately measuring millimeters of depth variation as well as a lack of studies to support the clinical significance of the findings.

Findings:

More research is needed to clearly identify ideal dosing, device and needle length for epinephrine administration via auto-injector. All guidelines recommend prescribing epinephrine injection devices for community use but there is a lack of unbiased data to suggest that one device is superior to another. While there is a new 0.1 mg device approved for infants 7.5-15 kg, most guidelines assert that the use of the 0.15 mg product is also appropriate in this weight range. Availability of a 0.15 mg and 0.3 mg epinephrine injection device on the National Core Formulary should provide appropriate coverage for people over 7.5 kg while assuring portability and avoiding excess cost.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References:

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