**STEP THERAPY POLICY**

**POLICY:** Epinephrine Auto-Injectors Step Therapy

**APPROVAL DATE:** 01/23/2019

**DRUGS AFFECTED:**
- Auvi-Q® (epinephrine injection, USP auto-injector – Kaleo)
- epinephrine auto-injector (authorized generics to EpiPen/EpiPen Jr – Mylan Specialty)
- EpiPen® (epinephrine injection, USP auto-injector – Mylan Specialty, generics)
- EpiPen Jr® (epinephrine injection, USP auto-injector – Mylan Specialty, generics)

**OVERVIEW**

Auvi-Q, epinephrine auto-injector (EpiPen/EpiPen Jr., generics), Adrenaclick, and the respective authorized generic products are epinephrine auto-injectors are indicated for the emergency treatment of severe allergic reactions (Type I) including anaphylaxis to stinging and biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances, and other allergens, as well as anaphylaxis to unknown substances (i.e., idiopathic anaphylaxis) and exercise-induced anaphylaxis.1-3 Brand Adrenaclick is no longer marketed; authorized generics to Adrenaclick (from Impax Laboratories) remain available.2,4 Symjepi™ (epinephrine injection, USP prefilled syringe) is a self-administered epinephrine prefilled syringe that has the same indication as the auto-injectors.20 Symjepi, Adrenaclick and its authorized generics are not targeted in this policy.

**Guidelines**

The World Health Organization, the World Allergy Organization (2011; evidence base update 2015), and parameters developed by the Joint Task Force on Anaphylaxis (representing the American Academy of Allergy, Asthma & Immunology [AAAAI], the American College of Allergy, Asthma & Immunology [ACAAI], and the Joint Council of Allergy, Asthma and Immunology) [2015] consider epinephrine to be an essential medication and the drug of choice for the treatment of anaphylaxis.5-9 Epinephrine is the only medication that reduces hospitalization and death when used in the management/treatment of anaphylaxis.5,7,9,10 There are no absolute contraindications to epinephrine use in anaphylaxis.1-3,6,8,11 Delays in administration have been associated with increased morbidity (e.g., encephalopathy due to hypoxia and/or ischemia), mortality, and the incidence of biphasic reactions (e.g., recurrent symptoms following resolution of initial manifestations).6,7,10,11 Patients who have experienced anaphylaxis should be prescribed self-injectable epinephrine if there is a continued risk for anaphylaxis.5,6 Currently, the optimal way of providing epinephrine treatment for anaphylaxis in the outpatient setting is through an auto-injector. The majority of patients should carry two auto-injectors, as many reactions will require two doses of epinephrine.

**Epinephrine Auto-Injector Devices**

All of the epinephrine auto-injectors are administered and dosed similarly.1-3 The auto-injectors are to be administered either intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Auvi-Q differs from the other auto-injectors in that it provides audible (electronic voice instructions, beeps) and visual (LED light) cues for use.5 Auvi-Q is also the only epinephrine auto-injector available as a 0.1 mg strength indicated in patients weighing 7.5 kg to 15 kg. Table 1 provides dosing and availability information for the epinephrine auto-injector devices. There are no clinical trials comparing the efficacy of the available epinephrine auto-injectors. However, a 2013 single-blind, crossover study compared the bioavailability of epinephrine injected via Auvi-Q or EpiPen in healthy
adults and found that a single injection of 0.3 mg epinephrine from either device resulted in similar peak and total epinephrine exposure.\textsuperscript{12}

### Table 1. Dosing and Availability of the Epinephrine Auto-Injectors\textsuperscript{13-15}

<table>
<thead>
<tr>
<th>Drug and Dosage Form</th>
<th>Dosing/Administration</th>
<th>How Supplied</th>
</tr>
</thead>
</table>
| **Adrenaclick\textsuperscript{®}**<br>(epinephrine injection, USP auto-injector [brand no longer available]; authorized generics)\textsuperscript{6} | | Each carton contains one trainer device and two prefilled auto-injectors containing epinephrine 1:1000:  
• 0.15 mg/0.15 mL  
• 0.3 mg/0.3 mL |
| **Auvi-Q\textsuperscript{®}**<br>(epinephrine injection, USP auto-injector) | Patients 7.5 kg to 15 kg: 0.1 mg IM or SC injection into the thigh.\textsuperscript{7}  
Patients 15 kg to 30 kg: 0.15 mg IM or SC injection into the thigh.\textsuperscript{7}  
Patients ≥ 30 kg: 0.3 mg IM or SC injection into the thigh.\textsuperscript{7} | Each carton contains one trainer device and two prefilled auto-injectors containing epinephrine 1:1000:  
• 0.1 mg/0.1 mL  
• 0.15 mg/0.15 mL  
• 0.3 mg/0.3 mL |
| **EpiPen\textsuperscript{®}**<br>(epinephrine injection, USP auto-injector; authorized generic) | Patients ≥ 30 kg: 0.3 mg IM or SC injection into the thigh.\textsuperscript{7} | Each carton contains one trainer device and two prefilled auto-injectors containing epinephrine 1:1000:  
• 0.3 mg/0.3 mL |
| **EpiPen Jr\textsuperscript{®}**<br>(epinephrine injection, USP auto-injector; generics; authorized generic) | Patients 15 kg to 30 kg: 0.15 mg IM or SC injection into the thigh.\textsuperscript{7} | Each carton contains one trainer device and two prefilled auto-injectors containing epinephrine 1:2000:  
• 0.15 mg/0.3 mL |

IM – Intramuscular; SC – Subcutaneous; \textsuperscript{7} For severe persistent anaphylaxis, repeat injections may be necessary. More than two sequential doses of epinephrine should only be administered under direct medical supervision; \textsuperscript{6} An S-ring to clip the two auto-injectors together is also provided.

### Needle Length

In the treatment of anaphylaxis, rapidly establishing high blood and tissue concentrations of epinephrine is critical.\textsuperscript{13} Studies have evaluated the pharmacokinetics and pharmacodynamics of epinephrine administered by either SC or IM injection in an attempt to determine the optimal route. It has been reported that IM administration (into the thigh) results in a faster time to maximum concentration (T\textsubscript{max}) and a higher C\textsubscript{max} compared with the SC route. Ensuring appropriate needle length of an auto-injector device to provide IM administration of epinephrine is a consideration. The FDA-approved self-administered injections have varying needle lengths; Table 2 provides the needle lengths for the self-administered epinephrine injectable products. A number of factors determine if epinephrine is delivered into the IM tissue of a patient, including the fat content of the patient and the compression of the overlying tissue upon drug administration, as well as the product’s needle length. Considerations may also vary based on patient gender and age. As a result of these factors, a needle that is too short may inadvertently deliver drug into the SC tissue; conversely, a needle that is too long may result in drug administration into the periosteum or the bone and could result in pain or bone damage.\textsuperscript{13,14} Several studies have evaluated the appropriate needle length for auto-injected epinephrine in pediatric patients with varying results. However, results of ultrasound studies generally indicate that currently marketed 0.15-mg EAs have needle lengths that may strike bone in ~29 to 43% of patients who weigh less than 15 kg and result in possible intraosseous injection.\textsuperscript{13,15,16}

### Table 2. Epinephrine Auto-Injector Needle Lengths\textsuperscript{14,17,19}

<table>
<thead>
<tr>
<th>Product</th>
<th>Needle Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 mg Auto-Injector</td>
<td></td>
</tr>
<tr>
<td>Auvi-Q 0.1 mg</td>
<td>0.74 cm</td>
</tr>
<tr>
<td>0.15 mg Auto-Injectors</td>
<td></td>
</tr>
<tr>
<td>Adrenaclick 0.15 mg</td>
<td>1.27 cm</td>
</tr>
</tbody>
</table>
Policy Statement
A step therapy program has been developed to encourage the use of a Step 1 product prior to the use of a Step 2 product. If the step therapy rule is not met for a Step 2 agent at the point of service, coverage will be determined by the step therapy criteria below. Note: Symjepi, brand Adrenaclick (no longer available) and the authorized generic to Adrenaclick (Impax Laboratories) are not targeted in this policy. All approvals are provided for 1 year in duration.

Automation: None

Step 1: epinephrine auto-injector 0.15 mg and 0.3 mg (generics to EpiPen/EpiPen Jr.), epinephrine auto-injector 0.15 mg and 0.3 mg (authorized generics to EpiPen/EpiPen Jr. from Mylan Specialty)

Step 2: Auvi-Q 0.1 mg, 0.15 mg, and 0.3 mg; EpiPen 0.3 mg, EpiPen Jr. 0.15 mg

Criteria
1. If the patient has tried a Step 1 product, then authorization for a Step 2 product may be given.

2. Exceptions can be made for Auvi-Q for patients or their caregivers who are blind or significantly visually-impaired.

3. Exceptions can be made for the Auvi-Q 0.1 mg strength auto-injector for patients who weigh < 15 kg (33 pounds).

4. Exceptions for other conditions or situations are not recommended.

References

**Other References Utilized**