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This clinical brief is sponsored by kaléo, Inc.

Clinical Considerations in the Management of Pediatric Anaphylaxis

The prevalence of food allergies has been increasing steadily in the US, and it remains a major public health concern.¹⁻⁴ Among the approximately 8% of children in the US with food allergies, 40% are allergic to multiple foods, according to results of a 2015-2016 household parent-proxy survey that involved 38,000 children.¹ Between 2008 and 2016, the rate of emergency department (ED) visits due to anaphylaxis—a potentially fatal allergic reaction—doubled in all patient groups (from 94 to 217 visits per million person-years) and tripled among children (from 54 to 163 visits per million person-years).² A large, multicenter retrospective cohort study of children who presented to pediatric EDs with anaphylaxis from 2016 through 2022 (N = 42,909) showed a yearly increase of 4.2% in ED admissions during this period.³ In 2013, the estimated direct annual medical cost associated with childhood food allergies in the US was \$4.3 billion—\$5.83 billion when adjusted to 2023 US\$.^{5,6} More current reviews of health care resource use relating to childhood food allergies in the US are based on these older cost estimates, which do not account for recently approved therapies.

Immediate administration of epinephrine can be life-saving in cases of anaphylaxis.⁷ Use of AUVI-Q® (epinephrine injection, USP), manufactured by Kaléo, is indicated in the emergency treatment of allergic reactions (type I), including anaphylaxis to allergens and idiopathic and exercise-induced anaphylaxis. AUVI-Q was designed with voice-guided instructions, visible cues, and an autoretractable needle that is contained in a compact device; it even reminds patients to seek emergency medical attention after use.^{8,9} This clinical brief describes the impact of anaphylaxis on the use of health care resources and associated costs and reviews the health-economic implications associated with AUVI-Q usage.

INDICATION

AUVI-Q® (epinephrine injection, USP) is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to allergens, idiopathic and exercise-induced anaphylaxis. AUVI-Q is intended for patients with a history of anaphylactic reactions or who are at increased risk for anaphylaxis.

IMPORTANT SAFETY INFORMATION

AUVI-Q is intended for immediate self-administration as emergency supportive therapy only and is not a substitute for immediate medical care. **In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care.** Each AUVI-Q contains a single dose of epinephrine for single-use injection. More than two sequential doses of epinephrine should only be administered under direct medical supervision. Since the doses of epinephrine delivered from AUVI-Q are fixed, consider using other forms of injectable epinephrine if doses lower than 0.1 mg are deemed necessary.

Please see the full [Prescribing Information](#) and the [Patient Information](#)

CONCERNS REGARDING EPINEPHRINE ADMINISTRATION IN CHILDREN

There is a need for specialized devices that deliver the appropriate dosage of epinephrine to pediatric patients who experience anaphylaxis. Historically-approved agents (HAAs), including epinephrine autoinjectors (EAIs), had dosages and needle sizes that were not optimized for use in small children weighing 16.5 to 33 lbs.¹⁰⁻¹³

Epinephrine administration to infants and toddlers can be challenging due to the size of these small patients. Although the suggested dosage of epinephrine is 0.01 mg/kg in these patients, a 0.15-mg dose of epinephrine may deliver a disproportionately high dosage for infants—a 2-fold dose for those weighing 16.5 lbs.¹⁰⁻¹²

Specific Concerns Regarding Needle-Related Epinephrine Autoinjector Injuries in Infants and Toddlers

A typical 0.15-mg EAI with a 12.7-mm needle may carry the risk of needle-related injuries because some small children have a shorter skin-to-bone depth at maximal pressure (STBD_{max}).^{12,13} Results of a 2012 to 2013 study of 100 pediatric patients (median age, 17 months) with food allergies who weighed less than 15 kg showed that 29% of patients had a STBD_{max} of less than 12.7 mm, indicating the potential for epinephrine injection into bone when HAAs are used.¹³

Furthermore, a 2017 study using ultrasonography to examine skin-to-muscle depth (STMD) and STBD in 53 infants and toddlers (weight range, 16.5-33 lb) highlighted concerning findings related to the use of HAAs.¹² A standard exposed needle length of 12.7 mm, as seen in 0.15-mg EAIs, could strike bone in 43.1% of infants and toddlers.¹²

AUVI-Q (epinephrine injection, USP) features an autoretractable needle that prevents users from reinserting the needle after epinephrine delivery, which is thought to help reduce the likelihood of accidental injuries.⁸ Additionally, AUVI-Q's injection mechanism minimizes the time that a needle contacts the patient's leg, requiring a hold time of 2 seconds and allowing injection completion in less than half a second. Importantly, the needle retracts and no longer is visible after injection.⁸

Clinical Considerations for Infants and Toddlers

In a retrospective study that used the OptumLabs Data Warehouse (which includes claims data for over 100 million commercial insurance and Medicare Advantage patients in the US), there was a 129.8%

increase in ED visits for anaphylaxis among children aged 0 to 4 years between 2005 and 2014; this indicates that the landscape of pediatric allergy management has undergone significant shifts.⁴

Until 2017, there were no FDA-approved epinephrine autoinjectors indicated for use in infants and toddlers weighing less than 33 lbs.^{12,14-18} Moreover, concerns regarding needle-related injuries linked to HAAs, which had a needle length of 12.7-mm, highlighted the necessity for alternatives and a gap in the market.^{12,13}

AUVI-q addresses this gap as the only FDA-approved epinephrine autoinjector specifically designed for infants and toddlers weighing 16.5 to 33 lb.¹⁴⁻¹⁸ This device features a needle length that is 40% shorter than that of the standard 0.15-mg EAI to better reduce the risk of bone contact in small children.

CONSEQUENCES OF DELAYED EPINEPHRINE ADMINISTRATION

The use of epinephrine is a critical intervention in cases of anaphylaxis; delay in its administration is associated with heightened risk of hospitalization, death, and other poor outcomes.^{11,19-22} Results of a 6-year study that examined the impact of early vs late administration of epinephrine following food-induced anaphylaxis (FIA) revealed that, during 384 ED visits for FIA, 30% of 234 pediatric patients did not receive their first dose of epinephrine until after arrival to the ED.²⁰ Patients who received early epinephrine (ie, before arrival to the ED) had a shorter median length of stay (3 vs 4 hours; $P = .003$) and were significantly less likely to be hospitalized than were those who were treated later (17% vs 43%, respectively; $P < .001$).²⁰ More recent studies published in 2017 and 2022 revealed that approximately 60% of patients 25 years or younger who presented with anaphylaxis to the emergency department had not received epinephrine before arriving at the ED.^{23,24}

Causes of Delayed and Improper Usage of EAIs

Delays in administering epinephrine often are attributed to factors related to EAIs. A 2018 survey conducted in 917 adults who had been prescribed an EAI for an allergy and/or who were parents of children prescribed an EAI for an allergy found that only about half of patients at risk of anaphylaxis have their prescribed autoinjectors available.²⁵ Moreover, some patients and caregivers may exhibit low confidence

IMPORTANT SAFETY INFORMATION (Continued)

AUVI-Q should **ONLY** be injected into the anterolateral aspect of the thigh. Do not inject intravenously, or into buttock, digits, hands, or feet. Instruct caregivers to hold the leg of young children and infants firmly in place and limit movement prior to and during injection to minimize the risk of injection-related injury.

Rare cases of serious skin and soft tissue infections have been reported following epinephrine injection. Advise patients to seek medical care if they develop any of the following symptoms at an injection site: redness that does not go away, swelling, tenderness, or the area feels warm to the touch.

and fear regarding use of EAIs.^{10,26} The potential for needle-related injuries may cause a fear of injection, leading to hesitation during emergencies.^{10,26,27} The results of a questionnaire given to more than 1200 Canadian parents of children who were prescribed an EAI showed that approximately 56% reported fear of using the device. The most commonly cited reasons for fear among the 65.4% of parents who further specified causes included concerns about hurting the child (34.6%), using the EAI incorrectly (32.5%), or a bad outcome or death (24.5%).²⁷

Improved education and training in device usage is critical. The results of a 2015 study (N = 102 participants) of the potential causes of improper EAI usage found that only 16% of participants used their EAI properly by completing all steps in manufacturers' instructions for use; among the remaining 84% of participants, more than half (56%) missed at least 3 steps. The most common error in use by patients was not holding the device in place for at least 10 seconds (76%).²⁸

USABILITY OF EPINEPHRINE AUTOINJECTORS: AUVI-Q (EPINEPHRINE INJECTION, USP) AND EPIPEN JR

The results of several studies support the usability of AUVI-Q in the management of anaphylaxis.⁹ An open-label, randomized, crossover, noninterventional human factors usability study of AUVI-Q was conducted in 2018, wherein 96 untrained adults (age, 18-65 years) used AUVI-Q 0.15 mg and EpiPen Jr 0.15 mg (epinephrine injection, USP; Mylan Specialty LP) trainers to simulate epinephrine administration to a child-sized manikin.⁹ The participants had no previous experience or training on how to use an injection device. Individuals with any potential experience in using an EAI or with any knowledge of injection devices were excluded from the study.⁹ Participants were only provided with written instructions on the device label and/or device voice instructions, mimicking real-life scenarios in which immediate and accurate action is crucial.⁹

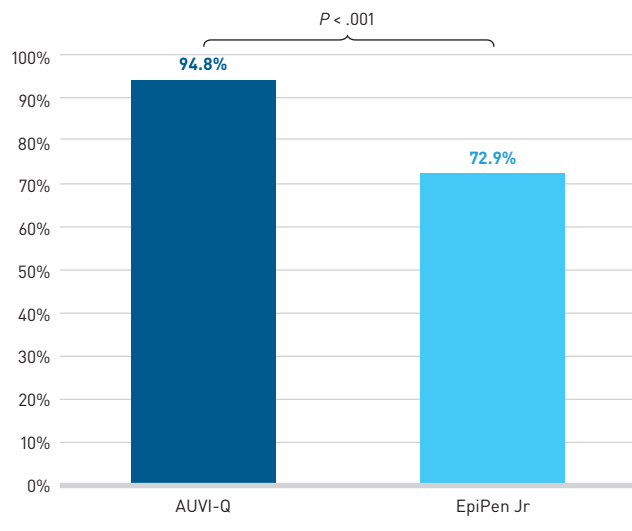
Following a simulation with 1 device (randomly chosen), participants encountered the same simulation with the other autoinjector, enabling a direct comparison of their performance.⁹ Results showed that the vast majority of untrained participants using AUVI-Q compared with those using EpiPen Jr completed all injection tasks (85.4% vs 19.8%, respectively; $P < .001$). Further, a significantly greater number

of untrained adults successfully completed key injection tasks with AUVI-Q compared with EpiPen Jr (94.8% vs 72.9%; $P < .001$) (Figure 1).⁹ The investigators also noted that accidental injection of epinephrine into the finger or hand would have occurred in none of the untrained adults using AUVI-Q and in 14.6% of those using EpiPen Jr ($P < .001$).⁹

ECONOMIC IMPACT OF AUVI-Q (EPINEPHRINE INJECTION, USP) IN COMMERCIAL CLAIMS DATABASE STUDIES

The economic impact of AUVI-Q compared with other EAIs was investigated in 2 commercial claims database studies; the results were presented at the Academy of Managed Care Pharmacy Nexus 2020 conference, held October 16 to 19, 2023, in Orlando, FL.²⁹⁻³² In both studies, AUVI-Q demonstrated lower overall costs of health

Figure 1. Percentage of Patients Who Completed Key Injection Tasks, by Epinephrine Autoinjector^{9,a}



*Key injection tasks defined as minimum tasks required for a patient to receive an epinephrine dose
N = 96

Study sponsored by kaleo, Inc.

IMPORTANT SAFETY INFORMATION (Continued)

Epinephrine should be administered with caution to patients with certain heart diseases, and in patients who are on medications that may sensitize the heart to arrhythmias, because it may precipitate or aggravate angina pectoris and produce ventricular arrhythmias. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or taking cardiac glycosides or diuretics. Patients with certain medical conditions or who take certain medications for allergies, depression, thyroid disorders, diabetes, and hypertension, may be at greater risk for adverse reactions. Common adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

care than did use of the other EAI devices in the 3-month follow-up period after an anaphylaxis event.

Cost-Effectiveness of AUVI-Q Compared With Other EAIs

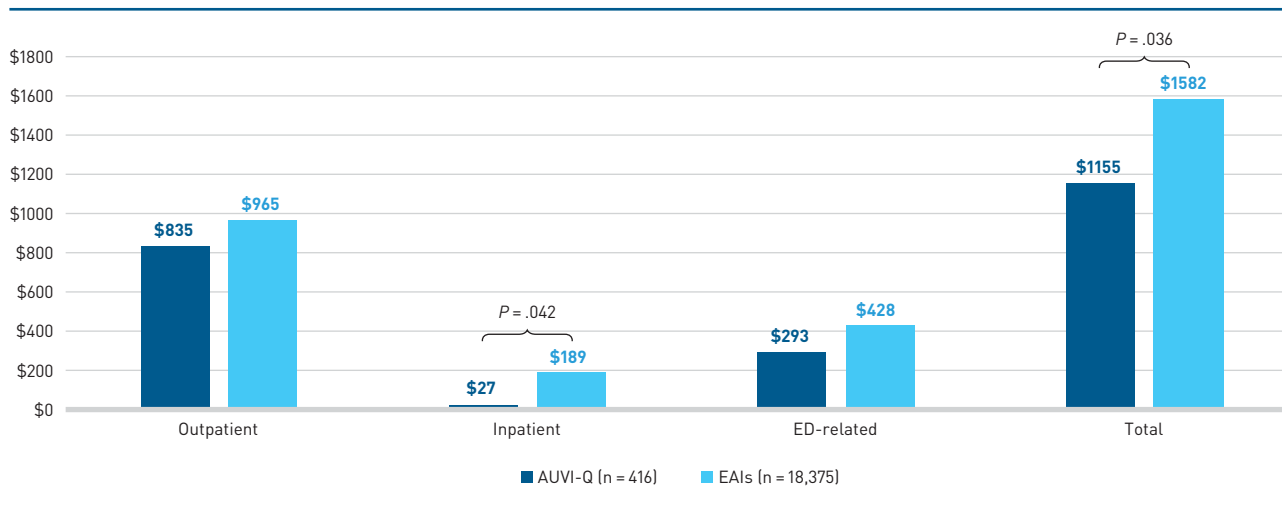
In the first study, a commercial claims analysis, health care resource use and costs of care were compared in 2 groups of patients with anaphylaxis during the 3-month period following an anaphylaxis event: those who were prescribed AUVI-Q and individuals who were prescribed other EAIs, both in matched and nonmatched patient populations.^{29,30}

The IBM® MarketScan® Commercial Database for claims and encounters (which included patient claims data from January 1, 2016, to October 31, 2019) was used to identify 18,791 patients who experienced anaphylaxis and were prescribed an EAI. This was determined based on a previously validated algorithm by Harduar-Morano et al and *International Classification of Diseases, Ninth Edition*

and *Tenth Revision* codes.^{29,30} Patients were assigned to a treatment cohort (AUVI-Q or other EAIs) based on the last EAI prescribed before the index date, set as the day of initial anaphylactic episode.^{29,30} There were 416 patients prescribed AUVI-Q and 18,375 patients prescribed other EAIs.^{29,30} Continuous medical and pharmacy coverage were required 12 months pre-index and 3-months post-index. A filled EAI prescription was required during the pre-index period.^{29,30}

The results of this study demonstrated the economic benefits of prescribing AUVI-Q for patients with anaphylaxis (Figure 2).^{29,30} Costs during the 3-month post-index period, excluding prescription expenses, were significantly lower in the AUVI-Q cohort than in the groups using other EAIs (\$1155 vs \$1582, respectively; $P = .036$) and amounted to a notable total savings in care costs of \$427 per patient.^{29,30} Particularly noteworthy was the significant decrease in inpatient costs totaling \$162 for AUVI-Q patients vs those using other EAIs (\$27 vs \$189; $P = .042$), a reduction that corresponded with the observed decline in hospitalizations among this cohort.^{29,30}

Figure 2. Average 3-Month Health Care Costs by Category for Patients Treated With AUVI-Q vs Other Epinephrine Autoinjectors From January 2017 to October 2019^{29,30}



EAI, epinephrine autoinjector; ED, emergency department.
Study sponsored by kaleo, Inc.

INDICATION

AUVI-Q® (epinephrine injection, USP) is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to allergens, idiopathic and exercise-induced anaphylaxis. AUVI-Q is intended for patients with a history of anaphylactic reactions or who are at increased risk for anaphylaxis.

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Furthermore, patients prescribed AUVI-Q exhibited reduced costs of care across outpatient, inpatient, and ED settings, although these differences did not reach statistical significance.^{29,30}

Use of AUVI-Q, therefore, provided an economic benefit—patients prescribed AUVI-Q incurred significantly lower total costs of care compared with those using other EAI during the followup period, an outcome independent of prescription expenses.³⁰ As previously indicated, this analysis also showed that the mean number of hospitalizations was significantly lower in the AUVI-Q cohort than in the group given another EAI (hospitalizations per total sample, mean [SD]: 0.003 [0.054] vs 0.018 [0.156], respectively; $P = .01$).²⁹ Notably, patients using AUVI-Q experienced significantly fewer laboratory and immunology referrals (0.6 vs 0.8; $P = .001$).²⁹

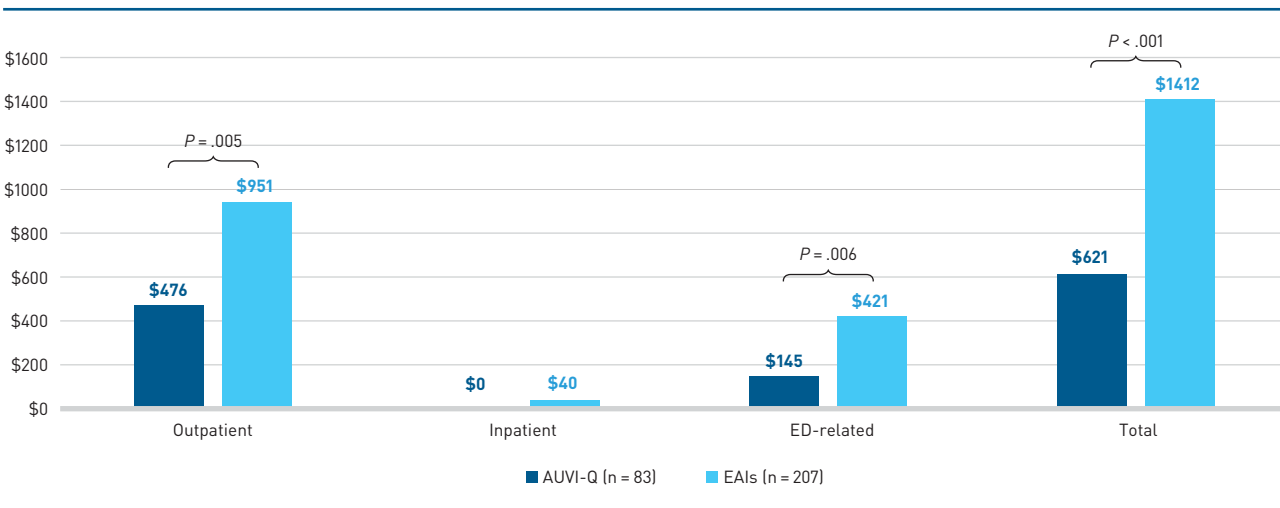
Cost Effectiveness Among Varying Severities

The objective of the second study, which included the same patient population and methods from the first study, was to compare

real-world costs of care for propensity score-matched (PSM) patients who experienced mild-to-moderate (I, IIA, IIB) or severe (IIIA, IIIB, IIIC) anaphylaxis and had been previously prescribed AUVI-Q (mild-to-moderate anaphylaxis, 83 patients; severe anaphylaxis, 166 patients) or another EAI (mild-to-moderate anaphylaxis, 207 patients; severe anaphylaxis, 406 patients).³¹

In the mild-to-moderate anaphylaxis subgroup, the AUVI-Q cohort displayed significant cost savings with total costs of care, excluding prescriptions, when compared with the other EAI cohort (\$621 vs \$1412, respectively; $P < .001$); this represented a cost savings of \$791 among the AUVI-Q cohort (Figure 3).^{31,32} This reduction was observed across various health care cost categories (eg, ED and outpatient visits), indicating less resource use by patients prescribed AUVI-Q.³¹ Additionally, patients prescribed AUVI-Q required fewer visits to the ED.³¹ In the severe anaphylaxis subgroup, AUVI-Q use also provided a significant cost benefit (Figure 4).³¹ The total costs of care, excluding prescriptions, for the AUVI-Q cohort compared

Figure 3. Average 3-Month Health Care Costs by Category for Patients With Mild-to-Moderate Anaphylaxis Treated With AUVI-Q vs Other Epinephrine Autoinjectors From January 2017 to October 2019^{31,32}



EAI, epinephrine autoinjector; ED, emergency department.

Study sponsored by kaleo, Inc.

IMPORTANT SAFETY INFORMATION (Continued)

AUVI-Q should **ONLY** be injected into the anterolateral aspect of the thigh. Do not inject intravenously, or into buttock, digits, hands, or feet. Instruct caregivers to hold the leg of young children and infants firmly in place and limit movement prior to and during injection to minimize the risk of injection-related injury.

Rare cases of serious skin and soft tissue infections have been reported following epinephrine injection. Advise patients to seek medical care if they develop any of the following symptoms at an injection site: redness that does not go away, swelling, tenderness, or the area feels warm to the touch.

with the other EAI cohort were \$1360 less per patient (\$1476 vs \$2836; $P = .024$).^{31,32} Notably, patients prescribed AUVI-Q experienced significantly fewer hospitalizations than did those using other EAIs (0.006 vs 0.035; $P = .023$).^{31,32}

In summary, regardless of anaphylaxis severity and independent of prescription costs, patients prescribed AUVI-Q had lower health care resource use and financial costs in the 3 months following an anaphylactic episode than did patients prescribed other EAIs.²⁹⁻³²

CONCLUSIONS

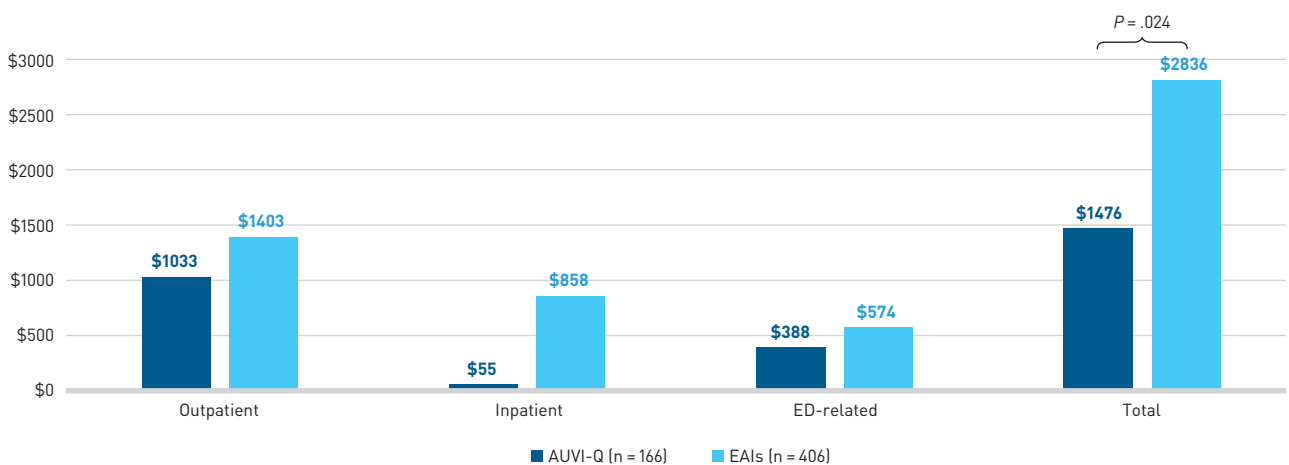
Anaphylaxis, with its rising incidence and potentially life-threatening nature, demands precise and effective interventions. AUVI-Q serves as a treatment option with its clinical value supported by the results of several studies that underscore its importance in the anaphylaxis and food allergy treatment landscape. By delving into the impact of different anaphylaxis treatment devices on health care resource use

and expenditures, this article provides valuable insights for health care professionals, policymakers, and patients. Ultimately, a thorough understanding of different clinical and economic factors is essential to optimize anaphylaxis management and treatment, ensure timely interventions, and improve outcomes for individuals facing this potentially life-threatening condition. •

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Figure 4. Average 3-Month Health Care Costs by Category for Patients With Severe Anaphylaxis Treated With AUVI-Q vs Other Epinephrine Autoinjectors From January 2017 to October 2019³¹



EAI, epinephrine autoinjector; ED, emergency department.
 Study sponsored by kaleo, Inc.

IMPORTANT SAFETY INFORMATION (Continued)

Epinephrine should be administered with caution to patients with certain heart diseases, and in patients who are on medications that may sensitize the heart to arrhythmias, because it may precipitate or aggravate angina pectoris and produce ventricular arrhythmias. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or taking cardiac glycosides or diuretics. Patients with certain medical conditions or who take certain medications for allergies, depression, thyroid disorders, diabetes, and hypertension, may be at greater risk for adverse reactions. Common adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

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IMPORTANT SAFETY INFORMATION (Continued)

Please see the full [Prescribing Information](#) and the [Patient Information](#).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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