

Anaphylaxis

Access to Epinephrine in Outpatient Setting



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KEYWORDS

• Epinephrine • Anaphylaxis • Costs • Price • Economics • EpiPen • Shortage

KEY POINTS

- Epinephrine autoinjectors (EAls) are expensive.
- Access to EAls is limited worldwide.
- Lower cost alternatives to EAls exist.

INTRODUCTION

Epinephrine is a lifesaving treatment of systemic allergic reactions (SARs) and anaphylaxis to foods, insect stings or bites, medications, and other allergens. Cox and colleagues¹ updated the World Allergy Organization (WAO) grading system for SARs as summarized in **Table 1** to clarify the early signs and symptoms of a SAR and to encourage the early administration of epinephrine. The term systemic allergic reaction applies to all grades of reactions with the term “anaphylaxis” appropriate for grades 4 or 5. The early use of epinephrine in SARs is important to maximize the likelihood of successful treatment, whereas delayed use is associated with increased incidence of death.^{2–4}

Epinephrine autoinjectors (EAls) were developed in the 1970s and first approved by the Food and Drug Administration (FDA) in the United States in 1987 (EpiPen, Mylan, Canonsburg, PA, USA). EAls available in the United States include EpiPen and its authorized generic (Mylan, Canonsburg, PA, USA); Auvi-Q (Kaléo, Richmond, VA, USA); as well as epinephrine injection USP autoinjector (Teva, Tel Aviv, Israel, and

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Table 1
Proposed modification of the 2010 World Allergy Organization grading system

Grade 1: Any of the Following Symptoms	Grade 2	Grade 3	Grade 4	Grade 5
Upper respiratory: Nasal symptoms: sneezing, rhinorrhea, nasal pruritus/congestion Cutaneous: Urticaria and/or erythema/warmth/pruritus other than localized at injection site, tingling of lips, angioedema (not laryngeal) Throat clearing/itchy throat Cough Tingling, itching of lips Angioedema (not laryngeal) Conjunctival erythema, pruritus, tearing Nausea Metallic taste	Symptoms/signs from ≥ 2 organ systems listed in grade 1	Lower airway: Mild bronchospasm, eg, cough, wheezing, shortness of breath, which responds to treatment and/or Abdominal: Abdominal cramps and/or vomiting/diarrhea and/or uterine cramps	Lower airway: Severe bronchospasm, eg, not responding or worsening in spite of treatment Upper airway: laryngeal edema with stridor	Lower or upper airway: respiratory failure Cardiovascular: collapse, hypotension, or loss of consciousness

Adapted from Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization Systemic Allergic Reaction Grading System: Is a modification needed? J Allergy Clin Immunol Pract. 2017;5(1):58–62.e5.

Parsippany, NJ, USA), Adrenaclick (Amneal Specialty), and the authorized generic of Adrenaclick, epinephrine injection, USP autoinjector (Impax Generics, Hayward, CA, USA/Amneal Pharmaceuticals, Bridgewater, NJ, USA). An epinephrine syringe developed as a lower-cost alternative is Symjepi epinephrine injection (Adamis Pharmaceuticals, San Diego, CA, USA). Other EAls available in Europe include Jext (ALK-Abelló Ltd, Berkshire, UK) and Emerade, developed by Medeca Pharma AB (Uppsala, Sweden) and produced/sold by Bausch & Lomb (Kingston upon Thames, UK). Emerade is available in Sweden, Norway, Denmark, Finland, France, Spain, the Netherlands, the United Kingdom, Ireland, and Germany. As of 2021, Emerade is seeking a partner to market this device in the United States.

Mylan's EpiPen intermittently has been in short supply since November 2017⁵; the FDA officially posted notice of this shortage on May 9, 2018.⁶ An editorial in *The Lancet*, October 2018, entitled "The EpiPen Shortage: How Has It Come to This?" reports on national shortages of the EpiPen in Australia, Canada, United States, and the United Kingdom. Some countries reported being completely out of stock of the "junior" version of the EpiPen indicated for younger children. Responses to the shortages include prescription of alternative EAls as listed earlier, permitting use of devices past their expiration date, prescribing only 1 rather than 2 EAls per subject, and reducing the minimum weight for use of the adult dose from 30 to 25 kg.⁵ The *Lancet* editorial challenges Mylan's explanation that its manufacturer, Meridian Medical Technologies, was fully responsible for the shortage and states that the reason for the shortage "remains a mystery."⁵ Furthermore, the editors point out that Mylan's dominance of the EAI market (90%) has public health consequences and ethical implications, when cost and availability become insurmountable barriers to access a lifesaving medication.⁵

Manufacturing issues have at times plagued most, if not all, companies that make EAls and these issues have contributed to EAI shortages. A voluntary recall of EpiPens occurred in 2018 due to 2 reports of "failure to activate the device due to a potential defect in a supplier component."⁷ In March 2020, the FDA issued a notice making consumers aware of potential malfunction of the EpiPen related to "device failure from spontaneous activation caused by using sideways force to remove the blue safety release, device failure from inadvertent or spontaneous activation due to a raised blue safety release, difficulty removing the device from the carrier tube, or user errors."⁸ A notice from the FDA dated June 1, 2020, warns consumers who "received" EAls manufactured by Impax/Amneal (Adrenaclick and its generic) after December 20, 2018, of a manufacturing issue.⁹ Consumers were instructed to inspect the product for lack of a yellow "stop collar," which is intended to prevent the devices from delivering a double dose of epinephrine. It is not clear if this manufacturing issue affected availability of Adrenaclick and its generic. Auvi-Q had a voluntary recall in 2015 due to potential dosing issues.¹⁰

Several factors limit the ability of newer products to garner and maintain market share versus Mylan's EpiPen. First, the EpiPen has name recognition. Second, training for the use of each device is different. To illustrate, the epinephrine injection, USP autoinjector from Amneal Pharmaceuticals/Impax Generics requires the removal of 2 caps rather than just 1. Although learning to use a new device can be challenging, novel design elements can improve safety and usability. An example is Auvi-Q, which has unique features including its rectangular shape intended to fit in a pocket, a retractable needle, and voice instructions. Untrained adults were more likely to use Auvi-Q correctly versus the EpiPen Jr, when given only written instructions and the voice instructions inherent in the Auvi-Q device.¹¹ Symjepi also has a compact design, compared with the EpiPen, and fits more easily into a pocket or purse. Third, insurance coverage differs for each EAI. According to the Managed Markets Insight and

Technology Database, the EpiPen had unrestricted access for 61% of commercial lives as of 2018.¹² In contrast, Auvi-Q had unrestricted access for “19% of commercial lives in all locations” among these same commercial health plans. Even though Auvi-Q was not covered by as many commercial insurance plans, the manufacturer offers it with \$0 to \$25 copayment to all commercially insured subjects and has a patient assistance program for uninsured and Medicaid subjects. Fourth, EAls are rated “BX” by the FDA indicating that “data that have been reviewed by the Agency are insufficient to determine therapeutic equivalence” and when ordered may not be substituted by a pharmacist one for another.¹³ Therefore, if a health care professional prescribes an “EpiPen,” the pharmacist is obligated to prescribe the Mylan brand. One issue that has not yet been addressed in the literature is the ease of ordering different EAls in the electronic medical record (EMR). When health care professionals order EAls, they may use the term EpiPen due to brand familiarity, and other brands of EAls may or may not be easily searchable or even included in the EMR ordering system.

The annual direct costs in the year 2010 in the United States for EAls were estimated to be \$294 million, accounting for about 25% of the \$1.2 billion annual cost to treat SARs including anaphylaxis.^{14,15} The average wholesale price (AWP) and wholesale acquisition cost (WAC) of each EAl is included in [Table 2](#), except for the Auvi-Q. Accurate wholesale pricing for the Auvi-Q is not available because it is distributed through a single specialty pharmacy network and one commercial pharmacy to minimize costs. Many of the products’ AWP and WAC have not been updated since 2015 to 2016; the most recent AWP and WAC available data are presented. Costs for the EpiPen were relatively stable until Mylan acquired this product from Merck (Kenilworth, NJ, USA) in 2007. The AWP since that time for 2 EpiPens increased 545% from \$113.27 to \$730.33 as of 2016, based on the most recent AWP available.¹⁶ This price increase persists even after accounting for inflation ([Fig. 1](#)).^{16,17} Although the out-of-pocket expenses for individual subjects may have decreased since the public outcry about EpiPen costs in 2016, the effective date of the most recent AWP available is May 16, 2016, and does not reflect the impact of price cuts or patient assistance programs.¹⁶ Another source of costing data called ProspectoRx, published by Elsevier, promises “real-time” drug pricing, but academic institutions typically do not have access to this resource. Marketing information for Symjepi provides WACs for several devices as of December 2020 and cites ProspectoRx as the source¹⁸; however, the WACs derived from ProspectoRx in this document are identical to those listed in the Redbook, with dates ranging from October 1, 2015, to January 16, 2019. Therefore, it is unlikely that new WAC or AWP have been posted for the EAls in the United States since the Redbook values available at the time of this writing.

Use of the AWP is controversial, but it is often used as a proxy for societal cost in cost-effectiveness analyses.¹⁹ An economic analysis published in 2011 used the 2006 to 2007 AWP of the EpiPen to estimate the annual cost of EAls for food-induced SARs. According to the International Society for Pharmacoeconomics and Outcomes Research good research practices guidelines from 2010, “Pharmaceutical prices used in the vast majority of cost-effectiveness analyses are either based on average wholesale prices (AWPs) in the United States or government-negotiated prices in Europe. The former are not only imperfect measures of actual prices paid (eg, ignoring discounts and rebates), but may also greatly overestimate societal opportunity costs because of the implicit inclusion of producer surplus created through patent-protected monopoly pricing.”²⁰ In summary, AWP is used as an approximation for societal drug costs, despite its limitations. The United States Department of Veterans Affairs Health Economics Resource Center (HERC) discusses the challenge of

Table 2
Average wholesale prices and wholesale acquisition costs for epinephrine autoinjectors, epinephrine prefilled syringes, and epinephrine kits in the United States

Manufacturer	Drug Name	NDC Number	Pkg Size	Dose	AWP Pkg price(US\$)	WAC	Effective Date
Mylan	EpiPen	49502-0500-02	2s ea	0.3 mg/0.3 mL	730.33	608.61	May 16, 2016
Mylan	EpiPen Jr.	49502-0501-02	2s ea	0.15 mg/0.3 mL	730.33	608.61	May 16, 2016
Mylan	Epinephrine injection, USP autoinjector	49502-0102-02	2s ea	0.3 mg/0.3 mL	375	300	December 15, 2016
Mylan	Epinephrine injection, USP autoinjector	49502-0101-02	2s ea	0.15 mg/3 mL	375	300	December 15, 2016
Kaleo	Auvi-Q	60842-0022-01	2s ea	0.15 mg/0.15 mL	n/a*	n/a*	n/a
Kaleo	Auvi-Q	60842-0023-02	2s ea	0.3 mg/0.3 mL	n/a*	n/a*	n/a
Adamis ^a	Symjepi epinephrine injection	00781-3442-20	2s ea	0.3 mg/0.3 mL	312.5	250	January 16, 2019
Teva	Epinephrine injection, autoinjector	00093-5986-27	2s ea	0.3 mg/0.3 mL	693.81	300	November 27, 2018
Teva	Epinephrine injection, autoinjector	00093-5985-27	2s ea	0.15 mg/0.3 mL	693.81	300	August 20, 2019
Amneal Specialty	Adrenaclick	52054-0804-02	2s ea	0.3 mg/0.3 mL	553.12	460.93	October 1, 2015
Amneal Specialty	Adrenaclick	52054-0803-02	2s ea	0.15 mg/0.15 mL	553.12	460.93	October 1, 2015
Amneal/Impax	Epinephrine injection, autoinjector	54505-0102-02	2s ea	0.3 mg/0.3 mL	494.01	395.21	October 1, 2015
Amneal/Impax	Epinephrine injection, autoinjector	54505-0101-02	2s ea	0.15 mg/0.15 mL	494.01	395.21	October 1, 2015
Certa Dose, Inc ^b	Epinephrine convenience kit	71754-0001-01	1 mL	1mg/mL	89.99	89.99	November 26, 2018
Focus Health Group ^b	Epinephrine Snap-V	24357-0911-01	1 ea	1mg/1 mL	156	130	June 16, 2016

Abbreviations: n/a, not available; NDC, National Drug Code; Pkg, package.

* Accurate AWP and WAC for Auvi-Q were not available.

^a At the time of this Redbook listing, Symjepi was distributed by Sandoz. Adamis reacquired rights of manufacturing, commercialization, and distribution on May 11, 2020.

^b These products are available only for licensed health care professionals to administer in a health care setting.

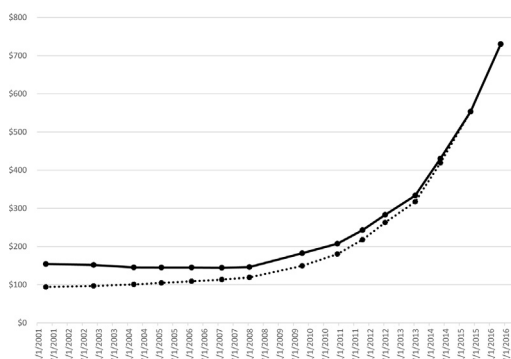


Fig. 1. AWP for the EpiPen 2001 to 2016. AWP of an EpiPen 2-pack or AWP of 2 EpiPens when sold individually, 2001 to 2016. The dotted line represents AWP in actual US dollars. The solid line represents AWP in constant year 2016 US dollars to adjust for inflation. Data were obtained from the Red Book Online System¹⁶ and converted into constant US dollars using the Consumer Price Index for medical care from the US Bureau of Labor Statistics.⁴⁵ The most recent AWP available was effective date May 16, 2016 (verified August 12, 2021).

determining medication costs for research purposes. The HERC states, “We recommend using 121% of the drug costs reported in the Federal Supply Schedule, 152% of the VA cost, or 64% of AWP. To find the cost of a generic label prescription drug, we recommend using 27% of AWP.”¹⁹ Federal Supply Schedule prices are publicly available.²¹ WACs, which have other methodologic advantages and disadvantages, may also be used to compare prices among different medications.²²

Decision analysis software (TreeAge Pro, Williamstown, MA, USA) has been used to evaluate the cost of generic EAI versus the EpiPen using a model that tracked spending for individual subjects over 20 years, with the assumption that each subject needs two 2-packs yearly, one each for home and school or work.²³ The cost for the EpiPen over a 20-year model duration totals \$58,667 (95% confidence interval [CI], \$57,745–\$59,588) versus \$45,588 for the generic EAI (95% CI, \$44,873–\$46,304). The model also incorporates other food allergy-related costs, such as specialist visits, grocery costs, and loss of work time for parents of food-allergic children. These costs are assumed to be the same for all subjects regardless of the type of EAI prescribed.

Cost-effectiveness analyses (CEAs) are computer simulations that incorporate the cost of, for example, a medication or a procedure, and the benefits of said intervention, often measured in quality-adjusted life years (QALYs) gained. A CEA published in 2021 found that prescribing 2 EAI to all subjects with a history of peanut allergy was not cost effective; however, among patients with a history of *anaphylaxis* to peanut, prescribing 2 EAI was more cost-effective.²⁴ The investigators therefore suggest limiting the second EAI to patients with a history of *anaphylaxis* to peanut. The incremental cost of prescribing a second EAI to all patients with peanut allergy was US \$10 million per QALY. Allergists/immunologists in clinical practice, however, know that SARs to food can be unpredictable, that the severity of prior SARs does not necessarily predict the severity of future SARs, and that subjects without a history of anaphylaxis may need 2 doses of epinephrine to manage a SAR. A 2020 review of epinephrine use in anaphylaxis states that all patients at risk for anaphylaxis should carry 2 EAI.²⁵ A European Academy of Allergy and Clinical Immunology task force

on the clinical epidemiology of anaphylaxis surveyed experts and found that 68% of experts prescribe only 1 device, whereas 32% prescribe 2 devices.²⁶ The investigators point out a lack of consensus that needs to be resolved and note that prescribing habits were affected by the patient's past medical history. Shortages of EAls have also contributed to prescribing habits, with some health care professionals prescribing only one EAl instead of 2 in times of shortage.⁵

Research demonstrates that subjects do not always fill their prescriptions when medical professionals prescribe EAls, and that cost is a factor in subject decision making. Only 50% of subjects prescribed epinephrine on discharge from pediatric emergency rooms filled the prescription in one study.²⁷ The impact of copayments, coupons, and assistance programs on prices at the pharmacy counter requires further research. Pourang and colleagues²⁸ (2017) found that copayments did not affect the likelihood of an EAl being dispensed once it was prescribed in the Kaiser Permanente Health Maintenance Organization. However, although the investigators indicate that nearly 30% of copayments exceeded \$30, they did not consider higher copayments. Data are not available on prescription:dispense ratios for subjects with exceedingly high copayments or for uninsured and underinsured subjects who can pay retail prices. More than 50% of EpiPen prescriptions are abandoned or not filled when the cost exceeds \$300 for a 2-pack.¹⁴ Two generic EAls manufactured by Mylan have an AWP of \$375. Two generic EAls manufactured by Impax Generics have an AWP of \$494.01. Subjects with any commercial insurance plan receive Auvii-Q for \$0–\$25 copayment through Walgreens pharmacy or the specialty pharmacy network, ASPN Pharmacies LLC (200 Park Avenue, Suite 300, Florham Park, NJ 07932, USA. (973) 295-3289) that distributes Auvii-Q. Kaléo, which manufactures Auvii-Q, works with this organization to reduce costs associated with traditional distribution routes. All uninsured subjects who make less than \$100,000 annually and Medicaid-eligible subjects can apply to a patient assistance program through Kaléo. Symjepi is the most affordable epinephrine device on the US market, perhaps owing to its simpler design.

Socioeconomic factors impact access to EAls. Children from high-income versus lower-income homes are 8.35 times more likely to be prescribed EAls.²⁹ Medicaid-enrolled children are less likely to receive EAls before arrival at an emergency department.³⁰ In another study, white versus non-white children were more likely to receive epinephrine early during a SAR.³¹ Early use of epinephrine is defined as epinephrine administered before arrival to the emergency department. Owning an EAl greatly increased the odds of early epinephrine treatment (odds ratio, 12.67; 95% CI, 4.46–35.96). The investigators did not assess insurance status but indicate that this finding suggests that there might be an economic influence on access to EAls.³¹ Fleming and colleagues³¹ examined the out-of-pocket costs for medications associated with food allergy and found higher costs for Caucasian and higher-income subjects. The investigators hypothesize that Medicaid-enrolled children may have lower out-of-pocket costs, that is, lower copayments. To reduce or eliminate insurance copayments, Fromer¹⁴ suggest that epinephrine be classified as a preventive medicine by the US Preventive Services Task Force (USPSTF).

The price of EAls also affects school districts and communities. The Michigan legislature mandated that all public schools stock EAls in 2014. The legislature estimated the cost for 2 EAl 2-packs, one adult and one pediatric, at \$140, whereas the “recently reported costs for commercial sources” was \$1200, according to the investigators. The annual calculated cost to Michigan public schools based on these 2 cost estimates ranges from \$565,460 to \$4,846,800.³²

A 2007 WAO survey of its House of Delegates indicates that EAls are available in 59% of 44 countries surveyed.³³ A 2020 study by Tanno and colleagues³⁴ found

that only 32% of the 195 countries in the world have access to EALs, which suggests that access may be decreasing over time. Those without EALs may use other, albeit less convenient, methods for the self-administration of epinephrine.³⁵ These methods include the use of ampules of epinephrine 1:1000 (1 mg/mL) with an empty 1-mL syringe to be drawn up as needed or epinephrine prefilled syringes (EPSs) containing various amounts of epinephrine. Both options are much less expensive than EALs; for example, an ampule of epinephrine 1:1000 (1 mg/mL) (Hospira, Lake Forest, IL, USA) has an AWP of \$2.52 and retail price of approximately \$12.¹⁶ Both options also allow for tailored dosing of epinephrine, greater than or less than the standard 0.15 mg or 0.3 mg doses contained in most FDA-approved EALs.

The ability to tailor dosing can theoretically be beneficial for children weighing less than 15 kg (33 pounds) or for large or obese subjects. Of note, in November 2017, the FDA approved an infant version of the Auvi-Q, Auvi-Q 0.1 mg, for children weighing 7.5 to 15 kg (16.5–33 pounds). This version has a shorter needle and a smaller dose of epinephrine (0.1 mg, vs 0.15 mg contained in other “junior” products). This is the only EAL available for infants and toddlers weighing less than 15 kg.

Low-cost alternatives to EALs are needed, and a few are discussed here. Symjepi (Adamis, San Diego, CA, USA) is an EPS that contains 0.3 mg epinephrine (or 0.15 mg, for patients weighing 15–30 kg) with a user-friendly design; it was approved by the FDA in June 2017 for subjects 30 kg (66 pounds) or more, and the 0.15 mg dose followed. The Ana-Kit (Hollister-Stier Laboratories, Spokane, WA, USA), which is no longer available, consisted of a syringe filled with 1 mL epinephrine 1:1000 (1 mg/mL) housed in a protective case for subcutaneous injection before it was removed from the US market.^{36,37} The Ana-Kit syringe had 0.1-mL graduations so that smaller doses could be administered depending on the subject’s age. The instructions recommended the following doses: “Adults and children over 12 years: 0.3 mL; 6–12 years: 0.2 mL; 2–6 years: 0.15 mL; Infants to 2 years: 0.05 to 0.1 mL.”³⁸ An appropriate dose could be administered by pushing the syringe plunger until it stopped. A second dose could be administered as appropriate, after rotating the rectangular plunger one-fourth turn to the right, to line up with a rectangular slot in the syringe.³⁸ An advantage of the prefilled Symjepi syringe is that it is housed in a dark blue plastic encasement to protect the epinephrine from ultraviolet light degradation. Epinephrine degrades with exposure to ultraviolet light, oxygen in ambient air, and excessive heat.^{39–41} EPSs stored at room temperature in a pencil box maintain acceptable US Pharmacopeia concentrations (90%–115% of label claim), pH, and sterility for 3 months.³⁵ The stability is limited to 2 months in high-temperature and low-humidity climates.^{35,42} In addition, some physicians and other health care professionals provide subjects with EPSs wrapped in aluminum foil,^{41,43} and these can be transported in a crush-resistant eyeglass case.

More affordable epinephrine convenience kits have been developed for use by emergency medical technicians and other health care professionals. Snap Medical Industries (Dublin, OH, USA) has developed EpinephrineSnap-V (a kit containing a vial of epinephrine 1:1000 [1 mg/mL] and empty syringes) and the EpinephrineSnap convenience kit (a kit containing an ampule of epinephrine 1:1000 [1 mg/mL] and empty syringes). The Focus Health Group, located in Knoxville, TN, USA, was contracted to commercialize these products. The AWP of this product is \$156,¹⁶ although information from company officials states that the average prices of EpinephrineSnap EpinephrineSnap-V are \$80 and \$130, respectively, with discounted group purchasing organization pricing available (personal communication, EWC, November 1, 2017). Another epinephrine convenience kit is manufactured by Certa Dose, Inc, with an

AWP of \$89.99 (see [Table 2](#)). Use of these options may not be as practical as is an EAI. The reason is that an epinephrine ampule or vial with an empty syringe requires more skill to properly draw up the epinephrine and administer it under emergency circumstances. Parents of individuals with a history of a SAR take longer to draw up epinephrine from an ampule (average 142 ± 13 seconds) compared with emergency department nurses (29 ± 0.09 seconds; $P < .05$).⁴⁴ The epinephrine dose drawn up by parents also ranged 40-fold when compared with 2-fold for emergency department nurses.⁴⁴ This is not an exhaustive list of epinephrine syringes and convenience kits available to health care professionals. These kits do not alleviate the cost or availability burden for the average consumer.

The rising cost of EAI has made self-administered epinephrine potentially unavailable to some subjects. Lower-cost alternatives such as EPSs are entering the US market. EAI have advantages, such as ease of use, but they are expensive, and shortages of EAI exacerbate the problem of access. Some EAI manufacturers strive to improve patient access via innovative distribution mechanisms that bypass complex incentives, which can drive up prices. Classifying EAI as USPSTF preventive medicines, or adding them to the World Health Organization Model List of Essential Medicines, could improve access by reducing or eliminating copayments.³⁴

CLINICS CARE POINTS

- Epinephrine is a lifesaving medication when used early to manage systemic allergic reactions
- EAI and EPSs facilitate epinephrine administration
- EAI are expensive, and costs have increased exponentially since 2007
- EAI are not available in every country, and shortages of EAI have exacerbated the problem of access
- EPSs such as Symjepi are a lower-cost alternative to EAI
- The only product available for infants weighing 7 to 15 kg is the Auvi-Q 0.1 mg EAI
- Prescribing 1 rather than 2 EAI is common and is at least partly a response to cost and access limitations
- Global access to EAI and EPSs is an equity issue that needs to be addressed by policymakers

DISCLOSURE

The authors report no conflicts of interest in this work.

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