

The High Cost of Epinephrine Autoinjectors and Possible Alternatives



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Epinephrine autoinjectors provide potentially life-saving therapy for pediatric and adult subjects with systemic allergic reactions, including anaphylaxis. However, the cost of these devices, specifically the EpiPen (Mylan, Canonsburg, Pa), is increasing exponentially. Epinephrine autoinjectors are commonly prescribed in the United States but are not readily available worldwide. Alternatives for the self-administration of epinephrine exist and should be considered for patients who cannot afford or do not have access to these devices. The epinephrine prefilled syringe, stored in an eyeglass or pencil case, is a safe and viable option for the self-administration of epinephrine. Epinephrine prefilled syringes may not be as ideal as using autoinjectors but are superior to patients living without access to this medication. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:665-8)

Key words: Epinephrine; Epinephrine autoinjectors; Anaphylaxis; Systemic allergic reaction; Cost; Price; Prefilled syringe; Ampule

INTRODUCTION AND COST OF EPINEPHRINE AUTOINJECTORS

Epinephrine is a potentially life-saving therapy for pediatric and adult subjects with systemic allergic reactions, including anaphylaxis.^{1,2} Epinephrine autoinjectors became available for patients in United States in 1980, with the introduction of the EpiPen (Mylan, Canonsburg, Pa).^{3,4} The cost of these devices is increasing, despite the vital nature of autoinjectors and their availability in the United States for over 35 years.⁵ Costs were relatively stable, accounting for inflation, until Mylan acquired the EpiPen in 2007 from Merck (Kenilworth, NJ). Between 2007 and 2016, the average wholesale price of 2 EpiPens increased 545%, from \$113.27 to \$730.33.⁶ The exponential

price increase persists even after accounting for inflation (Figure 1).^{6,7} The cost of epinephrine autoinjectors has become such an issue that the American Academy of Pediatrics Annual Leadership Forum included “Reducing the High Cost of Epinephrine Auto-Injectors” as one of their top 10 resolutions for 2016.⁸

EPINEPHRINE AUTOINJECTOR AWARENESS

The high price of epinephrine autoinjectors, specifically the EpiPen, is again a popular topic in the media. An online petition to investigate and regulate the price of the EpiPen has resulted in more than 140,000 letters sent to Congress.⁹ Senators have petitioned Mylan to decrease the price, with some success in the form of expanded patient assistance programs, savings card promotions, and plans to offer a less expensive, generic version of the EpiPen.¹⁰⁻¹² Epinephrine autoinjector prescriptions are on the rise in the United States, with approximately a 70% increase in EpiPen prescriptions from 2003 to 2010, partially due to increased awareness about the need for autoinjectors.¹³ In addition, the US School Access to Emergency Epinephrine Act of 2013 incentivizes schools to stock epinephrine, and several state laws require schools to stock epinephrine.¹⁴ Many patients or parents purchase multiple epinephrine autoinjectors to keep at work, school, relatives’ houses, and on their person.¹⁵ Autoinjectors expire and must be replaced frequently. For subjects who do not have insurance or have insurance plans with high deductibles, the costs add up quickly.

EXISTING US EPINEPHRINE AUTOINJECTORS

All epinephrine autoinjectors are not created equal in regard to price or administration technique. As of October 2016, 2 epinephrine autoinjector devices are available on the US market, the EpiPen and the authorized generic of Adrenaclick, called the epinephrine injection, USP autoinjector (Lineage Therapeutics, Horsham, Pa).^{3,16,17} The brand named Adrenaclick was discontinued, according to representatives at Impax Laboratories (Hayward, Calif), the company that acquired Lineage Therapeutics and Amedra Pharmaceuticals (Horsham, Pa, the former manufacturer of Adrenaclick) in 2015 (Impax Laboratories representatives, oral communication, August 30, 2016).¹⁸ Reintroduction of the Auvi-Q (Kaléo, Richmond, Va) autoinjector is planned for 2017.¹⁹ Of the 2 available autoinjectors, the EpiPen is more familiar to patients, physicians, and the general public and is perceived as easier to use. The generic autoinjector is still expensive, with an average wholesale price of \$494.01 for a 2-pack in 2015 and requires a different technique for use, with the removal of 2 caps, which may be more confusing to patients accustomed to the EpiPen.^{6,16} Epinephrine autoinjectors are rated “BX” by the US Food and Drug Administration, meaning “data that have been reviewed by the Agency are insufficient to

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Abbreviations used
EPS- Epinephrine prefilled syringe

determine therapeutic equivalence” and may not be substituted for one another by a pharmacist.^{20,21}

EPINEPHRINE AUTOINJECTOR AVAILABILITY AND ALTERNATIVES

The appeal of epinephrine autoinjectors is their convenience, stability, and ability to reliably administer a fixed dose of epinephrine, removing most human error. Epinephrine autoinjectors are commonly prescribed in the United States but are not readily available worldwide. In 2007, epinephrine autoinjectors for children and adults were available in 59.1% of 44 countries surveyed, based on responses from allergy/immunology specialists in the World Allergy Organization House of Delegates.²² However, even when obtainable, data on accessibility, based on costs and distribution, are not available. In other words, it is unknown how much of a given population in these countries can afford or have ready access to autoinjectors. Countries without access to autoinjectors use other methods for the self-administration of epinephrine.²³ These alternative methods include ampules of epinephrine 1:1000 (1 mg/1 mL) with an empty syringe to be drawn up as needed and prefilled syringes containing epinephrine. Both options are less expensive than autoinjectors; a 1 mg/mL ampule of epinephrine (Hospira, Lake Forest, Ill) has an average wholesale price of \$2.52 and retail price of approximately \$12.⁶ Both options also allow for tailored dosing of epinephrine, above or below the standard 0.15 mg or 0.3 mg dose provided by autoinjectors, which may be beneficial for children weighing less than 15 kg or obese and larger subjects.

Ampules of epinephrine with an empty syringe

The disadvantage of prescribing an epinephrine ampule with an empty syringe is that more skill is required to properly administer the medication in an emergency as compared with autoinjectors. Parents of patients with anaphylaxis take significantly longer to draw up epinephrine from an ampule (average 142 ± 13 seconds) as compared with emergency department nurses (29 ± 0.09 seconds) ($P < .05$).²⁴ The epinephrine content of doses drawn up by parents also ranged 40-fold as compared with 2-fold for emergency department nurses.²⁴ Therefore, the training required to draw up the correct dose of epinephrine from an ampule may be too complicated for many patients. Although the ampule and syringe is a less reliable method for epinephrine self-administration, it is an option for health care professionals. Institutions in Utah are supplying health care professionals with kits containing epinephrine syringes and ampules rather than autoinjectors to reduce costs.²⁵

Prefilled syringes containing epinephrine

Because of concerns over the skill required to draw up the correct dose of epinephrine in an emergency, epinephrine prefilled syringes (EPSs) are a more attractive option for subjects who cannot afford or do not have access to epinephrine autoinjectors. Indeed, the EPS is not a new concept. Before it was removed from the US market, the Ana-Kit (Hollister-Stier Laboratories, Spokane, Wash) contained a sterile syringe filled

with 1 mL of epinephrine (enough for a repeat dose) housed in a protective case for subcutaneous injection.^{26,27} A new product, the Epinephrine Prefilled Syringe (Adams Pharmaceutical Corporation, San Diego, Calif), containing epinephrine 0.3 mg in a single dose syringe, is under review by and received a Complete Response Letter from the US Food and Drug Administration.²⁸ Physicians may resort to prefilling syringes in clinic or asking pharmacists to fill syringes with the appropriate amount of epinephrine. However, concerns exist regarding the stability and sterility of EPSs because epinephrine degrades with exposure to ultraviolet light, oxygen in ambient air, and excessive heat.^{3,29,30} Epinephrine autoinjectors stored at 70°C for 10 days contained $62.6\% \pm 2.2\%$ of labeled epinephrine concentration and delivered $77.7\% \pm 3.3\%$ of labeled dose.³⁰ The package insert for the EpiPen recommends storage at 20°C to 25°C with excursions permitted to 15°C to 30°C and protection from light using the carrier tube provided.³

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.²³ Even at higher than recommended temperatures, EPSs stored at 38°C maintain acceptable US Pharmacopeia concentrations for 3 months at high (95%) humidity and 2 months at low (15%) humidity.³¹ Epinephrine appears to be safe from degradation in colder temperatures that remain above freezing.²⁹ Furthermore, EPSs can easily be protected from light by storing them in an eyeglass or pencil case. Although ultraviolet light degrades epinephrine, indoor light bulbs may not. One study found no difference in epinephrine concentrations in prefilled syringes stored in darkness or constant exposure to a 40-W light bulb after 5 months.³¹ Therefore, with proper precautions, EPSs appear to be stable, sterile, and safe for 3 months even in warmer climates. However, in climates with high temperatures and low humidity, the stability is limited to 2 months.^{23,31}

Studies examining the safety and efficacy of self-administered EPSs for the treatment of anaphylaxis are not available in the literature. Randomized controlled trials examining the use of epinephrine administration by any route for the treatment of anaphylaxis in human subjects have not been done because of obvious ethical constraints. EPSs, filled the same day, are effective to treat systemic allergic reactions in the office setting.³² Other potential limitations include unintentional disconnection of the needle from the syringe, accidental needle pricks, or premature release of the medication. Safety concerns also exist for autoinjectors. Leg lacerations and accidental injections leading to digit ischemia are reported.^{33,34} Patients may also not be willing or able to administer an EPS to themselves or their children. However, the same is true for autoinjectors. Only 29% of parents administered EpiPens for recurrent anaphylactic reactions in their children.³⁵

Education and teaching is required for the use of both EPSs and autoinjectors, although EPSs may require more training. Only 42% to 43% of patients are able to correctly administer autoinjectors 6 weeks after training according to the manufacturer's instructions and a technique demonstration.³⁶ Subjects can be taught to self-inject medication intramuscularly, as evidenced in the headache, arthritis, and contraception literature. Methotrexate and gold can be safely administered intramuscularly at home for treatment of rheumatoid or psoriatic arthritis.³⁷ Two 20-minute training sessions, on average, were required to ensure proper

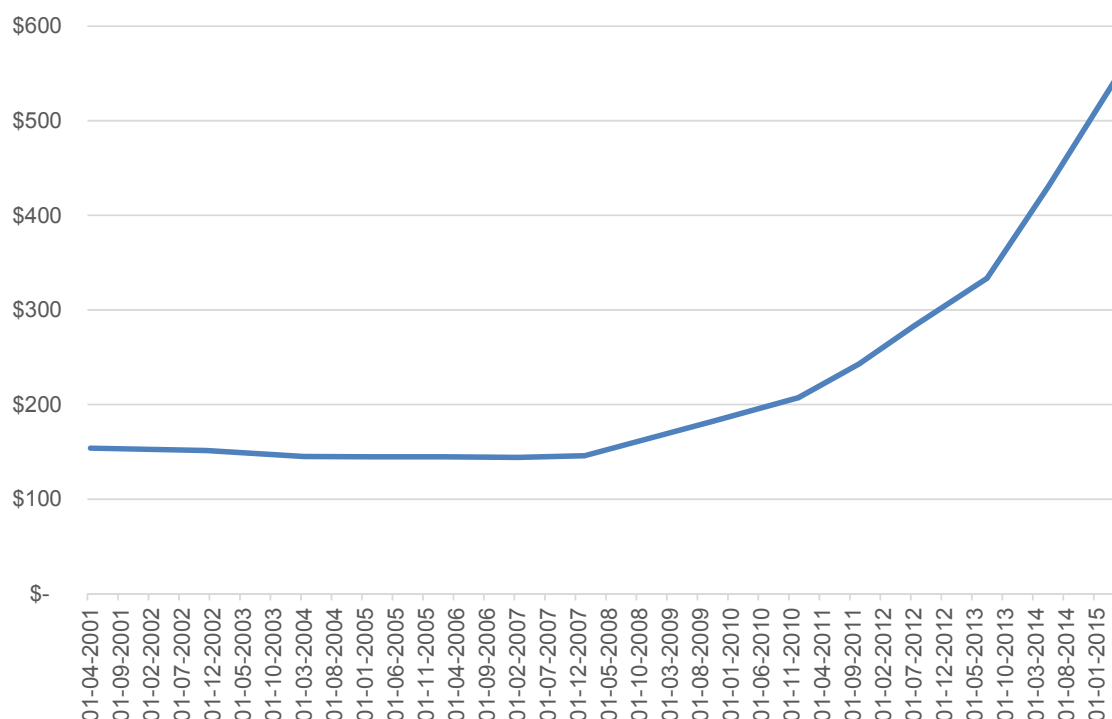


FIGURE 1. Average wholesale price of an EpiPen 2-pack, or average wholesale price of 2 EpiPens when sold individually, 2001-2015, in constant 2015 US dollars to adjust for inflation. Data were obtained from the Micromedex RED BOOK and converted into constant US dollars using the Consumer Price Index for medical care from the US Bureau of Labor Statistics.^{6,7}

administration including drawing up the medication from an ampule. Eighty-five percent (34 of 40) of subjects reported no problems with self-injection, 5% (2 of 40) had dosing errors that did not result in adverse events despite the toxicity of methotrexate, and 12.5% (5 of 40) reported local reactions at the injection site.³⁷ Self-administration of intramuscular ketorolac tromethamine and dihydroergotamine for migraine treatment is safe and efficacious.^{38,39} Furthermore, 8 out of 10 women prefer self-administration of intramuscular contraceptives over in-office administration.⁴⁰

CONCLUSIONS

In a perfect world, epinephrine autoinjectors would be readily obtainable and affordable for all subjects at risk of systemic allergic reactions, including anaphylaxis. In reality, these devices are too often out of reach for patients due to high cost or lack of availability. Although steps are being taken to reduce costs, the EPS, stored in an eyeglass or pencil case, is an option for the self-administration of epinephrine. Most consensus guidelines recommend the prescription of autoinjectors for subjects at risk of anaphylaxis, if available.^{41,42} Therefore, subjects opting for EPSs in the United States ideally should sign a waiver acknowledging that this option is less ideal than autoinjectors (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). EPSs should be replaced frequently (3 months in most climates, 2 months in climates with high temperatures and low humidity) and may be less convenient than autoinjectors. As with autoinjectors, patients and/or parents must be taught and trained how to use EPSs by physicians and other health care professionals. Providing patients with EPSs may not be as ideal as using

autoinjectors but is superior to patients living without access to this potentially life-saving medication.

Public announcements of decreased costs for some epinephrine autoinjectors from manufactures have been made since this paper was accepted for publication, however, the paper remains relevant because of the decreased costs of EPSs vs autoinjectors, and because autoinjectors are not yet available or affordable in many parts of the world.

REFERENCES

1. Bagg A, Chacko T, Lockey RF. Reactions to prick and intradermal skin tests. *Ann Allergy Asthma Immunol* 2009;105:400-2.
2. Phillips JF, Fox RW, Ledford DK, Glaum M, Lockey RF. Systemic reactions to subcutaneous allergen immunotherapy and the response to epinephrine. *Allergy Asthma Proc* 2011;32:288-94.
3. EpiPen and EpiPen Jr, Prescribing information. May 2016. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019430s061lbl.pdf. Accessed August 22, 2016.
4. Lockey SD. A new method of administering aqueous epinephrine: the EpiPen, an automatic syringe. *J Asthma Res* 1980;17:153-5.
5. Westermann-Clark E, Fitzhugh DJ, Lockey RF. Increasing cost of epinephrine autoinjectors. *J Allergy Clin Immunol* 2012;130:822-3.
6. Red Book Online System (electronic version). Greenwood Village, CO: Truven Health Analytics. Available from: <http://www.micromedexsolutions.com/>. Accessed August 25, 2016.
7. United States Department of Labor, Bureau of Labor Statistics. Consumer Price Index. Available from: <http://www.bls.gov/cpi/>. Accessed August 29, 2016.
8. American Academy of Pediatrics. Champion E-Correspondence. April 2016. Available from: https://www.aap.org/en-us/Documents/practicesupport_champion_e_correspondence_april2016.pdf. Accessed August 17, 2016.
9. Stop the EpiPen price gouging. Available from: <http://www.petition2congress.com/20720/stop-epipen-price-gouging/>. Accessed August 22, 2016.
10. Pollack AN. Mylan to offer a generic EpiPen at half the price. August 29, 2016. Available from: <http://www.nytimes.com/2016/08/30/business/mylan-generic-epipen.html>. Accessed August 29, 2016.

11. Mylan taking immediate action to further enhance access to EpiPen® (Epinephrine Injection, USP) auto-injector. August 25, 2016. Available from: <http://newsroom.mylan.com/2016-08-25-Mylan-Taking-Immediate-Action-to-Further-Enhance-Access-to-EpiPen-Epinephrine-Injection-USP-Auto-Injector>. Accessed August 25, 2016.
12. Scott E. Cost of EpiPen: one senator's daughter is Mylan CEO, another's needs drug. August 24, 2016. Available from: <http://www.cnn.com/2016/08/24/politics/epipens-congress-response/>. Accessed August 24, 2016.
13. Campbell RL, Manivannan V, Hartz MF, Sadosty AT. Epinephrine auto-injector pandemic. *Pediatr Emerg Care* 2012;28:938-42.
14. Epinephrine at school. July 6, 2016. Available from: <http://www.foodallergy.org/advocacy/epinephrine-at-school>. Accessed August 30, 2016.
15. Bilaver LA, Kester KM, Smith BM, Gupta RS. Socioeconomic disparities in the economic impact of childhood food allergy. *Pediatrics* 2016;137:e20153678.
16. Epinephrine injection, USP auto-injector [package insert]. Horsham, PA: Lineage Therapeutics Inc.; April 2013. Available from: <http://www.epinephrineautoinject.com/pdf/Prescribing-Information.pdf>. Accessed August 24, 2016.
17. Sanofi US issues voluntary nationwide recall of all Auvi-Q due to potential inaccurate dosage delivery. February 2016. Available from: <https://www.auvi-q.com/>. Accessed August 25, 2016.
18. Impax completes acquisition of Tower Holdings, Inc. And Lineage Therapeutics Inc. March 10, 2015. Available from: <http://investors.impaxlabs.com/Media-Center/Press-Releases/Press-Release-Details/2015/Impax-Completes-Acquisition-Of-Tower-Holdings-Inc-And-Lineage-Therapeutics-Inc/>. Accessed August 29, 2016.
19. Kaleo announces 2017 U.S. return of Auvi-Q® (Epinephrine Injection, USP) auto-injector for life-threatening allergic reactions. October 26, 2016. Available from: <https://www.kaleopharma.com/kaleo-announces-2017-u-s-return-of-auvi-q-epinephrine-injection-usp-auto-injector-for-life-threatening-allergic-reactions/>. Accessed October 31, 2016.
20. U.S. Food and Drug Administration. Orange Book preface. June 10, 2016. Available from: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm>. Accessed August 26, 2016.
21. U.S. Food and Drug Administration. Drugs@FDA Drug Database. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed August 29, 2016.
22. Simons FE. Epinephrine auto-injectors: first-aid treatment still out of reach for many at risk of anaphylaxis in the community. *Ann Allergy Asthma Immunol* 2009;102:403-9.
23. Kerddonfak S, Manuyakorn W, Kamchaisatian W, Sasisakulporn C, Teawsomboonkit W, Benjaponpitak S. The stability and sterility of epinephrine prefilled syringe. *Asian Pac J Allergy Immunol* 2010;28:53-7.
24. Simons FE, Chan ES, Gu X, Simons KJ. Epinephrine for the out-of-hospital (first-aid) treatment of anaphylaxis in infants: is the ampule/syringe/needle method practical? *J Allergy Clin Immunol* 2001;108:1040-4.
25. Chen D. Intermountain, University of Utah drop EpiPen for cheaper alternative. November 11, 2016. Available from: <http://www.deseretnews.com/article/865667020/Intermountain-University-of-Utah-drop-EpiPen-for-cheaper-alternative.html?pg=all>. Accessed November 16, 2016.
26. American Academy of Orthopaedic Surgeons. Allergic reactions and envenomations. In: Browner BD, Pollak AN, Gupton CL, editors. *Emergency care and transportation of the sick and injured*. 8th edition. Sudbury, MA: Jones and Bartlett Publishers. Available from: <https://books.google.com/books?id=xAPuKkKA6FEC&pg=PT459&lpg=PT459&dq=v=onepage&q&f=true>; 2002. Accessed August 25, 2016.
27. Auerbach PS. Allergic reaction. In: *Medicine for the outdoors: the essential guide to first aid and medical emergencies*. 5th ed. Philadelphia, PA: Mosby Elsevier. Available from: https://books.google.com/books?id=qG1eWyBe3_gC&pg=PA67&lpg=PA67&dq=v=onepage&q&f=true; 2009. Accessed August 29, 2016.
28. Adamis Pharmaceuticals receives Complete Response Letter from FDA for its epinephrine pre-filled syringe NDA. June 6, 2016. Available from: <http://ir.adamispharmaceuticals.com/phoenix.zhtml?c=99350&p=irol-newsArticle&ID=2175190>. Accessed August 25, 2016.
29. Parish HG, Bowser CS, Morton JR, Brown JC. A systematic review of epinephrine degradation with exposure to excessive heat or cold. *Ann Allergy Asthma Immunol* 2016;117:79-87.
30. Rachid O, Simons FE, Rawas-Qalaji M, Lewis S, Simons KJ. Epinephrine doses delivered from auto-injectors stored at excessively high temperatures. *Drug Dev Ind Pharm* 2016;42:131-5.
31. Rawas-Qalaji M, Simons FE, Collins D, Simons KJ. Long-term stability of epinephrine dispensed in unsealed syringes for the first-aid treatment of anaphylaxis. *Ann Allergy Asthma Immunol* 2009;102:500-3.
32. Wong PH, Adams KE, Carlson GS, Quinn JM. Experience with epinephrine delivery in immunotherapy-associated systemic reactions. *Ann Allergy Asthma Immunol* 2016;116:166-8.
33. Brown JC, Tuuri RE, Akhter S, Guerra LD, Goodman IS, Myers SR, et al. Lacerations and embedded needles caused by epinephrine autoinjector use in children. *Ann Emerg Med* 2016;67:307-315.e8.
34. Simons FE, Lieberman PL, Read EJ Jr, Edwards ES. Hazards of unintentional injection of epinephrine from autoinjectors: a systematic review. *Ann Allergy Asthma Immunol* 2009;102:282-7.
35. Gold MS, Sainsbury R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol* 2000;106:171-6.
36. Umasanthar T, Procktor A, Hodes M, Smith JG, Gore C, Cox HE, et al. Patients' ability to treat anaphylaxis using adrenaline autoinjectors: a randomized controlled trial. *Allergy* 2015;70:855-63.
37. Arthur AB, Klinkhoff AV, Teufel A. Safety of self-injection of gold and methotrexate. *J Rheumatol* 1999;26:302-5.
38. Turkewitz LJ, Casaly JS, Dawson GA, Wirth O, Hurst RJ, Gillette PL. Self-administration of parenteral ketorolac tromethamine for head pain. *Headache* 1992;32:452-4.
39. Weisz MA, el-Raheb M, Blumenthal HJ. Home administration of intramuscular DHE for the treatment of acute migraine headache. *Headache* 1994;34:371-3.
40. Stanwood NL, Eastwood K, Carletta A. Self-injection of monthly combined hormonal contraceptive. *Contraception* 2006;73:53-5.
41. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol* 2015;115:341-84.
42. Simons FE, Arduoso LR, Bilò MB, Dimov V, Ebisawa M, El-Gamal YM, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2012;12:389-99.

[TITLE OF CLINIC HERE]
Consent Form for Epinephrine in a Tuberculin Syringe

Dear Patient or Patient Representative,

You have informed us that you cannot afford or do not wish to pay the cost for epinephrine autoinjectors. Therefore, as an alternative, you are receiving two or more 1 cc tuberculin syringes, each with an attached needle, for self-injection of epinephrine. These syringes contain the equivalent amount of epinephrine as included in an autoinjector based on your weight.

You understand the risk/benefit of using these syringes versus an autoinjector. You also understand that the use of an autoinjector is quicker versus this alternative, which you have to self-inject into your anterior lateral thigh for a food-, drug-, or insect-induced or any type of systemic allergic reaction. A second dose may be administered in a similar fashion with a second syringe.

These syringes are protected by wrapping them in aluminum foil to avoid light. They should be kept in a hardened pencil or eyeglass case to protect them from being damaged. You also understand that they should be replaced every 2 to 3 months depending on the climate in your area. **IT IS YOUR RESPONSIBILITY TO DO SO.**

You declare that it is your choice to use this alternative versus an autoinjector and that you release this clinic and its physicians and other health care professionals from any and all liability for dispensing them and in their use.

If you have any questions, please seek the help of the nurse or physician.

Printed name of patient or minor

Date

Signature of patient or
responsible adult for minor

Date

Witness

Date

FIGURE E1. Sample consent form for epinephrine in a prefilled tuberculin syringe.

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