

Acute Care

ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

What price must we pay for safety? Excessive cost of EPINEPHrine auto-injectors leads to error-prone use of ampuls or vials and unprepared consumers



A series of recent events reported to ISMP has intensified our previously documented concerns about very serious errors with **EPINEPH**rine (www.ismp.org/sc?id=2780) that have occurred after healthcare providers felt compelled to replace cost-prohibitive **EPIPEN** (**EPINEPH**rine injection) auto-injectors or a generic **EPINEPH**rine auto-injector with ampuls and/or vials. When a severe hypersensitivity reaction occurs, the EpiPen or a generic auto-injector can help ensure that lifesaving **EPINEPH**rine is available quickly and is administered in the correct dose and by the correct route of administration. The device automatically delivers a premeasured dose of **EPINEPH**rine—0.3 mg for adults and 0.15 mg for children—intramuscularly (IM) or subcutaneously. But due to an ongoing series of price hikes, some healthcare providers have decided to use a much less costly alternative—**EPINEPH**rine ampuls and/or vials. Although cheaper, this method introduces a much higher risk of errors. As borne out by the ISMP National Medication Errors Reporting Program (ISMP MERP), the presence of a vial or ampul of **EPINEPH**rine invites dosing errors and accidental intravenous (IV) administration to a patient with an IV access catheter or IV administration set. Some errors have resulted in fatalities.

Recent errors

All of the recent events reported to ISMP involved administration of 1 mg of **EPINEPH**rine by the IV route after switching from EpiPens to **EPINEPH**rine ampuls and/or vials. For example, one hospital reported three errors in the past 6 months in which the entire contents of the 1 mg/mL vial of **EPINEPH**rine was administered IV, when 0.3 mg IM should have been administered. In another hospital, a patient who was experiencing an anaphylactic reaction to **FERRLECIT** (ferric gluconate) was also given **EPINEPH**rine 1 mg IV when the correct dose and route was 0.3 mg IM. The patient required admission to a critical care unit for close monitoring.

Available EPINEPHrine auto-injectors

Mylan's EpiPen is the most frequently prescribed **EPINEPH**rine auto-injector, generating more than 3.6 million outpatient prescriptions last year.¹ Several rival products joined the market only to fall by the wayside. EpiPen's strongest competitor, Sanofi's **AUVI-Q**, was removed from the market in October 2015 due to concerns about inaccurate delivery of the dose. A generic **EPINEPH**rine auto-injector by Impax (labeled as LineageTherapeutics, which Impax acquired) generated less than 200,000 prescriptions last year,² largely because prescribers are much more familiar with EpiPen. Also, the Impax product cannot be substituted as a therapeutic equivalent for EpiPen because the US Food and Drug Administration (FDA) has determined that there is insufficient data showing that the generic auto-injector is therapeutically equivalent. (The Impax product is not AB rated in the *Orange Book*.) The Impax auto-injector is not covered by some insurances, and purchasing groups have had difficulty negotiating contracts with the company. Thus, EpiPen essentially has a virtual monopoly on the market, contributing to ongoing price hikes over the years.

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SAFETY briefs



Burns during MRI from patches with metal in the backing. A nurse noticed that a patient about to have a magnetic resonance imaging (MRI) scan was wearing a fenta**NYL** transdermal system patch. She remembered that some patches have metal in the nonadhesive backing that is not in contact with the skin. She checked with the manufacturer, Apotex, and the company confirmed its patch had metal in its backing and was not MRI safe. Incidentally, an older

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Medicated patches with aluminum or other metal in their nonadhesive backing (as of July 2016)

Generic Name (Brand Name)	Manufacturer Name
clo NID ine transdermal system	Barr
clo NID ine transdermal system	Aveva
fenta NYL transdermal system	Aveva
lidocaine 70 mg/tetracaine 70 mg topical patch (SYNERA)	Galen
nitroglycerin transdermal system	Kremers Urban Pharmaceuticals
nicotine transdermal system (OTC) (HABITROL)	Dr. Reddy's Labs Inc.
nicotine transdermal system (OTC) (NICODERM CQ and NICODERM CQ CLEAR)	Sanofi Aventis/GlaxoSmith-Kline
nicotine transdermal system (OTC) (NICOTROL)	Boehringer Ingelheim
rivastigmine transdermal system (EXELON)	Novartis
rivastigmine transdermal system	Alvogen Malta
rotigotine transdermal system (NEUPRO)	UCB
scopolamine transdermal system (TRANSDERM SCOP)	GlaxoSmith-Kline/Novartis/Baxter
scopolamine transdermal system	Perrigo/Aveva
SUM Atriptan iontophoretic transdermal system (ZECUITY *)	Teva
testosterone transdermal system (ANDRODERM)	Allergan

*Sales voluntary suspended in June 2016 due to reported cases of serious application site reactions.

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High cost of EpiPens and other auto-injectors

According to pricing data provided in standard drug databases, the retail price of EpiPens, after adjustment for inflation, has increased by more than 450% since 2004,¹ going from about \$50 per pen in 2004 to more than \$300 per pen in 2016.² The price increases are among the biggest of any top-selling brand drug.³ Since two doses are often needed for severe allergic reactions, Mylan began providing two EpiPens per package (2-Pak) while discontinuing packages with a single pen. Some healthcare providers have reported paying up to \$900 for the EpiPen 2-Pak. By comparison, a 2-pack of EpiPens sold by Meda in France³ and Spain costs about \$85 (called “Altellus” in Spain). Price increases are not due to higher costs of the raw materials; a typical adult dose of **EPINEPHrine** packaged in a vial or ampul costs less than \$2. EpiPen price increases have also driven up the cost for alternative **EPINEPHrine** auto-injectors. The Impax product also carries a hefty price tag, with each twin pack costing between \$300 and \$500.

Dangerous and unethical pricing practices

We believe the excessive pricing of EpiPen and the generic auto-injector poses a serious threat to patient safety. Financially, the consumers’ ability to obtain and administer **EPINEPHrine** safely and efficiently during critical allergic responses is unduly impacted, placing adults and children with a history of serious allergies at significant risk if they can’t afford an auto-injector, even with insurance and company cost-savings cards that can reduce the cost of a 2-pack by up to \$100.⁴ Consumers are also relying on expired **EPINEPHrine** auto-injectors or hoping a single device will provide enough protection for multiple siblings or other family members. And, as detailed above, the high cost of EpiPen and the generic auto-injector has led healthcare providers to resort to the use of affordable alternatives that increase the risk of potentially deadly errors that would be much less likely with the auto-injectors.

Although we can’t say with certainty how many healthcare providers have switched or are switching to **EPINEPHrine** ampuls and/or vials (despite recommendations from various professional organizations to use the auto-injectors), we can’t fault them. For healthcare providers that use **EPINEPHrine** auto-injectors and store them in numerous locations throughout their organization, hundreds of thousands of dollars may be needed annually to stock these devices and replace them when they expire. (Mylan does not offer credit or replacement for expired EpiPens.) The pricing of EpiPens and alternative auto-injectors is unethical and socially irresponsible, and it’s reminiscent of the price gouging that was occurring with the gray market for drugs in short supply.

Anaphylaxis kits and simulation training

If your organization has made the difficult decision to replace **EPINEPHrine** auto-injectors with ampuls and/or vials, please consider providing patient care areas with an anaphylaxis kit rather than stocking the ampuls and/or vials separately. The kit should contain a 1 mL vial or ampul of **EPINEPHrine** 1 mg/mL, a syringe, and any other needed supplies (e.g., alcohol wipe, needle), along with clear directions regarding measurement of the correct dose and administration by the correct route. Simulation training using the kit is highly recommended to ensure practitioners are comfortable with and understand how to prepare and administer **EPINEPHrine** from a vial or ampul.

References

- 1) Swetlitz I. High price of EpiPens spurs consumers, EMTs to resort to syringes for allergic reactions. *STAT*. July 6, 2016. www.ismp.org/sc?id=2781
- 2) Miller M. There’s absolutely no reason why an EpiPen should cost \$300. *Slate: Money Box*. July 8, 2016; updated July 15, 2016. www.ismp.org/sc?id=2782
- 3) Koons C, Langreth R. How marketing turned the EpiPen into a billion-dollar business. *Bloomberg Businessweek*. September 23, 2015. www.ismp.org/sc?id=2783
- 4) Rubenfire A. Lack of competition leads to EpiPen pricing woes. *Modern Healthcare*. March 28, 2016.

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version of the prescribing information and displayed labels on *DailyMed* did not include a warning about this risk, which we asked the US Food and Drug Administration (FDA) to look into, although revised labels and prescribing information with the warnings were also accessible. Although the metallic component of this patch is nonferromagnetic and not attracted to the static magnetic field of an MRI system, aluminum and certain other metals found in the nonadhesive backing can conduct electricity and cause a burn during an MRI. In 2009, FDA issued a *Public Health Advisory* on this topic (www.ismp.org/sc?id=1762). An updated list of patches with metal in the backing is on **page 1**. Share this list with inpatient and outpatient radiology to guide the process when asking patients about patches before entering the MRI area.



Risk with entering a “test order.” Submitting a contrived prescription to a patient’s pharmacy to determine insurance coverage has led to close calls or actual dispensing of the medication to the patient. In one reported case, when a patient contacted a clinic for a warfarin refill, the nurse noticed that both warfarin and apixaban were on the patient’s medication list. Review of the notes in the electronic health record indicated that a “test script” had been sent to the pharmacy to determine the copay for apixaban. Apparently that prescription was dispensed, and the patient took both medications for about 3 days before the error was discovered. Luckily, no harm occurred. In another case, a pharmacy received an order for rivaroxaban for a patient with an active warfarin order. When the prescribing resident was notified about the therapeutic duplication, he stated that he only meant to see if the patient’s prescription would be covered by insurance. It may be that some prescribers don’t realize that pharmacies should not check this information by entering “test” orders (it violates their contract with vendors), or that the practice is dangerous as the patient may actually receive the medication. Instead, the patient, prescriber, or a hospital-assigned individual should call the insurance company or pharmacy benefits manager (PBM) to inquire about coverage.

Low dose enteral syringe tip gets FDA clearance

NeoMed and Medtronic have each received US Food and Drug Administration (FDA) 510(k) clearance for low dose tip ENFit syringes. NeoMed developed the low dose tip to address an earlier industry-wide problem concerning ENFit syringe deadspace and the associated concerns with dose accuracy when administering small volumes of medications. NeoMed has offered all syringe manufacturers royalty-free access to the design. Thus, other companies are now adopting this low dose tip design. The syringes, along with non-low dose ENFit syringes, are enabling the industry to finally get the new ENFit system on the market to minimize the dangers of accidental misconnections of enteral feedings and medications to intravenous access systems or other systems with a Luer connection. These low dose syringes will be available in sizes from 0.5 mL up to 6 mL. Larger syringes don't require the low dose tip because, as with all syringe types, larger capacity syringes should not be used for low dose amounts when accuracy is required.

The NeoMed 510(k) clearance includes enteral and oral use of its syringes. The ability to utilize a low dose or standard ENFit syringe for both oral and enteral delivery of liquid medications means that a facility may not necessarily have to maintain a separate inventory of oral syringes once they transition to ENFit. However, for smaller capacity syringes, there has been some concern expressed by neonatal practitioners about



Figure 1. Low dose tip syringe with flange to prevent accidental attachment to tracheostomy tube opening.

flanges near the syringe tips that have been added per ISO standard 80369-3 to mitigate accidental attachment to a tracheostomy tube opening (**Figure 1**). The flange may make it difficult to administer medications orally to neonates. To overcome the problem, NeoMed sells an add-on device called a "DoseMate" (**Figure 2**). We've learned that other efforts are underway to resolve the "flange" concerns. The Medtronic ENFit syringe does not have a flange at this time, but it's unclear how the company will respond to the ISO standard to prevent connection to a tracheostomy tube. Medtronic's initial clearance did not specify approval of its low dose ENFit syringe for oral use; however, the company has since submitted this claim to FDA and is awaiting 510(k) clearance.



Figure 2. NeoMed DoseMate add-on for oral administration for neonates.

Another issue is the lack of a child-resistant cap for use on over-the-counter (OTC) or prescription liquid medications for patients at home who have feeding tubes. Screw-on transfer lids (**Figure 3**) and plug-in stepped stoppers (**Figure 4**) are fine for pharmacy use but are not child resistant. We are told that companies are working to develop a child-resistant cap to prevent accidental overdose in homes where children may be present. In the meantime, in the home, use of an ENFit dosage straw in conjunction with a child-resistant bottle closure seems to be the way to go.



Figure 3. NeoMed screw-on transfer lid.



Figure 4. Medtronic plug-in stepped stoppers for bottles.

We are very hopeful that this transition will be successful. Vendors, regulators, standards groups, and others involved in the ENFit transition can learn from this experience to guide future implementation of other system connectors to prevent misconnections.

Special Announcements

ISMP accepting Cheers nominations

Nominations will be accepted through **September 9** for this year's **Cheers Awards**, which celebrate individuals and organizations that have set a standard of excellence in the prevention of medication errors during the previous 12 months. To submit a nomination, visit: www.ismp.org/sc?id=1777.

ISMP webinar

Join us on **September 29** for our next webinar, **Just Culture: Application of an Accountability Model with Medication Safety Events**. This program will explore the tenets of a Just Culture and how they can be applied to the investigation of medication safety events and accountability for safety. For details, visit: www.ismp.org/sc?id=349.

ISMP receives service award

In July, ISMP received the **2016 AACP Distinguished Service Award** from the American Association of Colleges of Pharmacy (AACP) for 20 years of outstanding leadership in medication error prevention and research. Mike Cohen, ISMP's president, credited clinical advisors and practitioners and consumers who report safety issues, stating: "Because of their efforts in keeping ISMP, FDA, and other oversight organizations informed about safety issues, thousands of medical product and practice improvements have occurred."

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