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Inside the Self-Injectable Epinephrine Sticker Shock

By: Sarah Adie, Pharm.D.

Background: Epinephrine autoinjectors have been used for decades to treat anaphylaxis resulting from a severe allergic reaction.[1] A two-pack of EpiPens® cost less than $100 in 2004. Since that time, Mylan has increased the price by more than 450%, raising the cost of a two-pack of EpiPens® autoinjectors to $600. The manufacturer has not provided specifics about this price increase. In response to an outcry from both consumers and government officials, a generic equivalent product was approved in December 2016.[2] Furthermore, several alternative epinephrine autoinjector products were approved in an effort to ensure patient access. Auvi-Q® recently rejoined the market in 2017 after being recalled in late 2015 by Sanofi Aventis following reports of unreliable administration of epinephrine doses.[3-4] This article answers various questions about currently available epinephrine autoinjectors.

What self-injectable epinephrine products are currently available?[5]

- EpiPen®, EpiPen Jr® (Mylan)
- Epinephrine Injection, USP (Impax)
- Epinephrine Injection, USP (Mylan)
- Auvi-Q® (kaléo)

These products are available as either 0.3 mg or 0.15 mg dosage forms.

What are the PROS and CONS of self-injectable epinephrine products?

EpiPen® (Mylan)

Pros: This product requires a one-step process for activation.[6] It only needs to be held in place for 3 seconds after activation.[7] The needle retracts after injection to prevent exposure to users. A trainer pen is provided with every prescription.

Cons: A shelf-life of 12 to 14 months may cause patients to discard unused products, increasing the cost burden. The two-pack design is bulky for users to carry.

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Selexipag for Pulmonary Arterial Hypertension

By: Ashley Ramp, Pharm.D.

Background: Pulmonary Arterial Hypertension (PAH) usually presents with symptoms of dyspnea, fatigue, and weakness due to vascular remodeling and decreased compliance of the pulmonary vasculature.[1] While the prevalence of PAH is estimated to be only 15-26 cases per million, it is associated with very high morbidity and mortality rates.[2] In the past 10 years, the number of pharmacological agents used to treat PAH has grown significantly.[3,4] This article will focus on one of the newest agents for PAH, selexipag (Uptravi®; Actelion) which was approved by the Food and Drug Administration (FDA) in December of 2015 for the treatment of patients with PAH, WHO class I, to delay disease progression and reduce the risk of hospitalization.[5]

Novel Oral Agent for PAH: Selexipag is a new oral agent for PAH with a unique mechanism of action (MOA).[6] While other prostanoids such as

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Epinephrine Injection, USP (Impax)

PROS: The product is the authorized generic version of Adrenaclick®, which is no longer on the market.[8] It has a longer shelf-life of 24 months and is less bulky than the EpiPen® autoinjector.[7,9]

CONS: This product should be held in place for 10 seconds after injection compared to 3 seconds with the EpiPen® brand and generic autoinjectors.[8] The product requires a two-step process for activation, and the needle does not retract. It is NOT considered bioequivalent to the EpiPen® autoinjector and is therefore NOT interchangeable. Trainers are only available if requested through the company. The cost is approximately $400 for a two-pack of autoinjectors.[7]

Epinephrine Injection, USP (Mylan)

PROS: This is the approved generic product of the EpiPen® autoinjector.[2]

CONS: Although less costly than the brand product, the cost is approximately $300 for a two-pack of pens.

Auvi-Q® (kaléo)

PROS: The product should be held in place for 5 seconds after injection, and audio directions instruct users on correct administration.[7] A trainer is supplied with each prescription that audibly guides users on accurate administration, even those who may not have been trained. The product is similar to the size of a thick credit card allowing for easy storage.

CONS: This product has the shortest shelf-life of the autoinjectors at 12 months or less, and it will cost cash payers $360 for a two-pack.[4] Complex insurance coverage is confusing for consumers and may limit accessibility.

Are expired EpiPen® products safe to use?

The Food and Drug Administration (FDA) warns to discard any outdated epinephrine autoinjectors.[10] However, a study published in 2000 found that at least 66% of the intended epinephrine dose of EpiPen® autoinjectors was maintained up to a year after expiration. Furthermore, in 2015 another study found EpiPens® retained more than 90% of the labeled dose up to 2 years after expiration. Finally, a study published in 2017 found that a majority of expired EpiPens® maintained at least 90% potency 5 to 44 months past their expiration dates.[11] Based on this limited data, the researchers suggest that outdated epinephrine autoinjectors could be used in a life-threatening anaphylactic reaction if no in-date products are available and that the process for establishing expiration dating for these products should be revised.

What is the Bottom Line?

Due to the high cost of brand-name EpiPen® and Auvi-Q®, the CCHS Formulary has switched from EpiPen® autoinjectors to Mylan's generic epinephrine injection. The State of Ohio has taken action to combat high prices with House Bill 101, which allows pharmacists to substitute prescribed, brand-name epinephrine autoinjectors for an equivalent generic epinephrine autoinjector for adults 18 years of age or older.[12] The bill also allows for pharmacists to dispense epinephrine autoinjectors to adults without a prescription under a physician protocol. The bill has gained support in the Ohio House of Representatives and is awaiting committee designation.

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epoprostenol (e.g., Flolan®, Veletri®) and treprostinil (e.g., Orenitram®, Remodulin®), serve as substrates for the inositol triphosphate (IP3) receptor, selexipag and its active metabolite act as direct IP3 receptor agonists; stimulation of the IP3 receptor leads to direct vasodilation of the pulmonary vasculature which helps to alleviate PAH symptomatology. Unlike other prostanoids which have relatively short elimination half-lives, selexipag's active metabolite has a half-life of up to 13.5 hours allowing for a much longer duration of action.[5]

Key Clinical Trial: Selexipag's FDA approval was based on the GRIPHON trial, an event-driven, multicenter, double-blind, placebo-controlled study that included 1156 patients with symptomatic, WHO Functional Class I-IV PAH.[6] Patients with PAH who were 18 to 75 years of age and had a pulmonary vascular resistance of at least 5 Wood units and a 6-minute walk distance (6MWD) of 50- to 450-meters were included. Treatment-naïve patients along with those receiving an endothelin-receptor antagonist (ERA) or a phosphodiesterase type 5 inhibitor (PDE-5I) at a stable dose for 3 months were included. However those receiving prostacyclin analogues were excluded. Patients were randomized to receive either selexipag (n=574) or placebo (n=582). The primary outcome in this time-to-event analysis utilized a composite endpoint of death, the occurrence of a PAH-related complication, and disease progression, whichever occurred first. Nearly all patients were WHO Functional Class II or III at baseline. The majority of the patients were being treated with a stable dose of an ERA (15%), PDE-5I (32%) or both (33%) at baseline. The selexipag group showed a 40% relative risk reduction (0.60; 99%CI, 0.46 to 0.78; P<0.001) of the primary composite endpoint. This decreased risk was primarily due to a reduction in hospitalization for PAH and disease progression, rather than mortality. Therefore, the authors concluded that the risk of the composite endpoint was significantly lower in patients treated with selexipag compared to those treated with placebo; however, there was no significant difference in mortality between the two groups.

Safety: The most common side effects of selexipag include headache, diarrhea, nausea, and jaw pain.[5] Unlike other PAH agents, selexipag is not associated with any Risk Evaluation and Mitigation Strategies (REMS) program. No contraindications are listed in its product labeling, but there is an important warning about Pulmonary Veno-Occlusive Disease (PVOD). Selexipag should not be used in those with severe hepatic dysfunction. Patients receiving selexipag should be monitored for hyperthyroidism.[7]

Dosing and Administration: The recommended starting dose of selexipag is 200 mcg twice daily.[5] Doses can then be titrated by 200 mcg at weekly intervals to a maximum of 1600 mcg twice daily. Patients with moderate hepatic impairment (Child-Pugh class B) should begin therapy at a dose of 200 mcg once daily. Doses can then be titrated by 200 mcg per dose at weekly intervals. Selexipag does not need to be renally dose adjusted. If treatment is delayed for 3 days or more, selexipag should be re-started at a lower dose and then retitrated. Selexipag tablets cannot be crushed, split, or chewed.

Availability and Cost: Selexipag tablets are available as 200-, 400-, 600-, 800-, 1000-, 1200-, 1400- and 1600-mcg strengths.[7] The medication also comes in a titration pack which contains 200 mcg (140 tablets) and 800 mcg (60 tablets) strengths; its average wholesale price (AWP) is about $26,136. The AWP of a 1-month supply of selexipag 200 mcg (60 tablets) is about $11,208, whereas a 1-month supply of all other strengths is about $17,424.

Role in Therapy: This agent could be considered as adjunctive therapy for patients who are still symptomatic and/or experiencing disease progression after optimization of other oral PAH agents, particularly ERAs and PDE-5Is.

Formulary Status: Selexipag was reviewed by the Critical Care Specialty Panel and will be evaluated by the CCHS Medical Staff Pharmacy and Therapeutics Committee at the end of June for final review and decision.

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