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With Advent of EVZIO for Lay Reversal of Opioid Overdose, Enthusiasm and Caution

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In July 2014, kaléo Pharmaceuticals launched its new product, EVZIO™—a naloxone hydrochloride drug–device combination—for the emergency treatment of opioid overdose.^{1,2} Similar to an automated external defibrillator, kaléo’s innovative product is programmed to guide an untrained lay user through the process of overdose reversal using prerecorded audiovisual prompts. It then automatically deploys an EpiPen®-like retractable mechanism to inject the opioid antagonist.

EVZIO’s significance is difficult to overstate. When the Federal Government announced its approval in April, it chose to do so through a conference call featuring the then Secretary of Health and Human Services Kathleen Sibelius, Acting Drug Czar Michael Botticelli, and Food and Drug Administration (FDA) Commissioner Margaret Hamburg. Calling EVZIO “an extremely important innovation,” Dr. Hamburg stressed that EVZIO received its approval almost 10 weeks ahead of schedule²—an FDA anomaly.

Though the federal response to the unprecedented overdose crisis has been sluggish,³ the rapid approval of EVZIO is certainly a positive development. This is the first naloxone product to be specifically user tested and labeled for prehospital lay administration. Its instructional features are designed to obviate the need for prior training on appropriate overdose response protocol, providing key information on basic life support and directing users to contact emergency medical response for follow-up care.² EVZIO also eliminates any assembly required in naloxone’s existing intramuscular (IM) or off-label intranasal (IN) delivery systems.

This product’s innovative elements make it an important new tool in the difficult struggle to curb the at least 21,000 annual opioid overdose fatalities.^{3–5} Although restricting the drug supply has been the prevailing retort to questions about providers’ role in addressing this

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crisis, endorsement of naloxone education and co-prescription with extended release and long-acting opioids is also evolving.⁶ When intended for individuals at possible risk of overdose, naloxone can be prescribed to family members, friends, caregivers, or other likely bystanders.² Pilot programs have generated positive evidence that such practices reduce fatality risk and may carry collateral benefits.^{3,7} Naloxone prescription at the point of practice has yet to gain wide adoption, however.³

Ongoing media coverage and considerable detailing efforts proposed by kaléo to market EVZIO are certain to inform and persuade more providers to engage in naloxone prescribing. This marketing strategy also includes formulating a risk assessment protocol to inform clinical decisions about when naloxone prescription may be appropriate. An algorithm that generates a naloxone prescription alert can be integrated into Risk Evaluation and Mitigation Strategy (REMS) trainings targeting opioid prescribers, electronic medical records, prescription drug monitoring programs, and other decision support systems.

Highly unusual for the FDA is that the product's labeling also implicitly expands the scope of possible prescription recipients beyond the at-risk patient. Prescribers are expressly encouraged to prescribe EVZIO to caregivers and others who is likely to witness and reverse an overdose. This may facilitate ongoing efforts to address health care providers' perceived malpractice liability risk for prescribing naloxone to third parties like parents and friends of possible victims; laws shielding providers for such practices are already on the books in about one third of all states.³ Media coverage and possible direct-to-consumer marketing efforts may also increase public awareness about naloxone in general and EVZIO in particular, boosting patient demand and pharmacy stocking formularies.

Outside of traditional healthcare settings, naloxone is also instrumental to community-based overdose prevention programs. These highly-promising initiatives by syringe exchange programs, parents' support groups, drug treatment facilities, and other organizations directly engage active and recovering drug users, their family members, service providers, police, and other non-medical first responders.⁸ Nevertheless, legal questions about third-party prescribing, deputation, and liability limit scale-up.³ FDA endorsement of third-party prescribing can mollify institutional concerns, while the product's automated features can cut training costs.

Naloxone access and prescription programs continue to be geographically constrained.⁸ Traditionally, these initiatives were primarily confined to urban areas or other places where they were bundled with programs targeting people who inject drugs—a population where overdose has been endemic.⁸ As these community access efforts have expanded coverage to prescription drug users, they have proliferated throughout the country, but their scope remains limited. In this context, EVZIO provides an opportunity for much broader reach, especially if the antidote can be dispensed through mail-order pharmacies, as kaléo intimates. This is especially critical for rural and tribal areas that may have sporadic provider access, but alarmingly high overdose rates.⁴

Despite these promising aspects, there are reasons to view the advent of this new tool with caution. EVZIO's suggested price tag ranges from approximately \$450–600,

notwithstanding the reality that naloxone is a generic medication that at times retails for less than \$7 per dose in the U.S. and as little as \$1 in Europe. Although third party payers will negotiate discounts and the bulk of the retail cost will be borne by health insurers in many cases, the product will likely prove too costly for resource-constrained community or local government distribution programs. Running until August 2016, the company's reduced-cost access program for lower-income patients provides out-of-pocket savings of up to \$100 off each qualifying prescription for EVZIO.

More importantly, the cost of this device and kaléo's evolving marketing efforts may impact the cost of existing or new naloxone products, including an IN delivery device now under development.⁹ This is because substantial elements of prescriber naloxone training and REMS materials created by drug companies are patentable.¹⁰ Although there is no indication of kaléo's intention to do so, pharmaceutical firms have used strategies based on intellectual property protections and inflated safety claims to restrict market competition.¹⁰

Over the past decade, there have been efforts to relax the regulatory requirements to access naloxone, but its prescription status remains a significant barrier.³ This is true for the drug's existing formulation and is likely to remain true for EVZIO. FDA signals to providers that they can prescribe the drug for use on third parties is rhetorically useful, but it is not clear if it is sufficient to nudge providers to engage in this practice. In addition, FDA statements do not supersede state law and local regulatory provisions governing third-party prescribing, nor do they automatically extinguish providers' concerns about the possible risk of malpractice liability.

Although over-the-counter (OTC) status of an affordable naloxone product would certainly facilitate access and advance overdose prevention, EVZIO is unlikely to enter the OTC space in the near future. On the face of it, this product is perfectly positioned for OTC sales: it was specifically user tested to be deployed without professional supervision. EVZIO's labeling substantially reduces prescribers' instructional and gatekeeper roles, uniquely situating the drug for broad distribution. Nevertheless, kaléo did not seek a "direct-to-OTC" approval. Given the millions invested in the development of EVZIO and its relatively high retail price, kaléo appears to have made the rational projection that the product's sales would not generate a sufficient return on investment without being covered by health insurance—something only prescription drug formulations confer.

While celebrating EVZIO's potential contribution, forward-looking efforts must be made to limit the ability of this and other new products to inhibit access and increase the cost of naloxone, whether to individuals or to third-party payers. Any patent protections and market exclusivity granted to naloxone formulations should be narrowly tailored so as not to crowd out existing products or prevent market entry for additional innovative and affordable options. The FDA and other federal agencies should encourage and facilitate the development of OTC products containing this drug.

Finally, it is important to emphasize that naloxone access—though vital—is only a stop-gap measure at the end of a chain of multiple system failures. In the minutes and hours after an overdose has occurred, this drug is extraordinarily effective in averting tragedy.

Nevertheless, ensuring its wider deployment must go hand-in-hand with efforts to develop a continuum of interventions that engage at-risk populations, their healthcare teams, and communities in effective drug treatment, supportive services, and other evidence-based interventions shown to prevent overdose events from occurring in the first place.

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