

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209862Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

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| Date | (electronic stamp) |
| From | Sharon Hertz, MD |
| Subject | Division Director Summary Review |
| NDA# | 209862 |
| Applicant Name | Kaleo, Inc. |
| Date of Submission | April 19, 2016 |
| PDUFA Goal Date | October 19, 2016 |
| Proprietary Name / Established (USAN) Name | Evzio / (naloxone hydrochloride injection) Auto-Injector for intramuscular or subcutaneous use |
| Dosage Forms / Strength | Autoinjector/ 2 mg |
| Proposed Indication(s) | <ol style="list-style-type: none"> 1. EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and /or central nervous system depression. 2. EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present. 3. EVZIO is not a substitute for emergency medical care. |
| Action: | Approval |

| | |
|------------------------------------|--|
| Material Reviewed/Consulted | |
| OND Action Package, including: | |
| Medical Officer Review | Elizabeth Kilgore, MD, Joshua Lloyd, MD |
| Pharmacology Toxicology Review | Carlic Huynh, PhD, Elizabeth Bolan, PhD, R. Dan Mellon, PhD |
| CMC Review/OBP Review | Pramoda Maturu, PhD, Ramesh Raghavachari, PhD/ Vincent (Peng) Duan, PhD, Haritha Mandula, PhD |
| CMC Microbiology Review | Daniel J. Schu, PhD, Stephen Langille, PhD |
| Clinical Pharmacology Review | Wei Qiu, PhD, Yun Xu, PhD |
| CDRH/ODE/DAGRID, GHDB | John McMichael, CDR Alan Stevens |
| CDTL Review | Josh Lloyd, MD |
| OSE/DMEPA | Mónica Calderón, PharmD, BCPS, Vicky Borders-Hemphill, PharmD, Quynh Nhu Nguyen, MS |
| OPDP/DCDP | L. Shenee Toombs, Regulatory Review Officer |
| OMP/DMPP | Morgan Walker, PharmD, MBA, LaShawn Griffiths, MSHS-PH, BSN, RN, Barbara Fuller, RN, MSN, CWOCN |

OND=Office of New Drugs

DMEPA=Division of Medication Errors Prevention

CDTL=Cross-Discipline Team Leader

DCDP=Division of Consumer Drug Promotion

DMPP=Division of Medical Policy Programs

ODE = Office of Device Evaluation

DAGRID = Division of Anesthesiology, General Hospital, Respiratory, Infection Control, & Dental Devices General Hospital Devices Branch

OSE= Office of Surveillance and Epidemiology

DSI=Division of Scientific Investigations

OPDP=Office of Prescription Drug Promotion

OMP=Office of Medical Policy Initiatives

CDRH= Center for Devices and Radiological Health

GHDB = General Hospital Devices Branch

Signatory Authority Review Template

Sections 1 through 11 of this review have been reproduced, verbatim, from the CDTL memo written by Dr. Josh Lloyd.

1. Introduction

Evzio (naloxone hydrochloride) is an autoinjector intended for subcutaneous or intramuscular injection that was approved in a 0.4 mg strength on April 3, 2014, under NDA 205787, for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Evzio is a single-use, drug-device combination product intended for use in the community. It is designed for use in non-healthcare settings by laypersons to rescue victims experiencing the life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention. Evzio was the first naloxone product approved in this setting.

Kaleo, Inc. (“Applicant”), submitted a supplemental new drug application (sNDA) to NDA 205787 for Evzio to add a 2 mg strength for their product for the same indication. The applications for the 0.4 mg product and the 2 mg product were subsequently split into two separate NDAs for the reasons stated in Section 12 of this review. The primary reviews were entered under NDA 205787.

The only difference between the proposed 2 mg formulation and the already-approved 0.4 mg formulation for Evzio is the concentration of naloxone hydrochloride (i.e., 5 mg/ml versus 1 mg/ml, respectively). All other excipients, volume of medication delivered (0.4 ml), and product components, including the container-closure system, are unchanged. The Applicant conducted the clinical development program under IND 112,292.

The original approval of Evzio was based on the submission of bioavailability data to reference the Agency’s previous finding of safety and effectiveness for Narcan (naloxone hydrochloride; NDA 16636), an injectable formulation of naloxone. Narcan was approved April 13, 1971, and is available for subcutaneous, intramuscular, and intravenous use for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine. Narcan has been discontinued from marketing; however, the Agency determined that it was not withdrawn from sale for reasons of safety or effectiveness (74 FR 22751).

The Applicant requested priority review status for this application. The request was based on the assertion that the higher dose of naloxone would represent a significant improvement in the safety or effectiveness of the treatment of opioid overdose, particularly in opioid overdoses involving mixed agonist/antagonists (citing literature that higher doses are required for buprenorphine-induced respiratory depression) as well as overdoses in infants and children

(citing the higher doses recommended by the American Academy of Pediatrics, as described in Section 2 of this review). Narcan nasal spray (4 mg intranasal spray) is a recently approved naloxone product for community use that results in naloxone exposures of approximately five times greater than that achieved with a 0.4 mg intramuscular injection (e.g., approximates the exposures achieved with a 2 mg injection). However, approval of a 2 mg strength of Evzio would offer an alternative route of administration to the nasal route while potentially still delivering similar higher exposures to naloxone as compared to a 0.4 mg intramuscular injection. Therefore, priority review status was granted for this application.

This review will explore in greater detail the data collected from the submitted bioavailability study to evaluate the naloxone exposures achieved with the 2 mg strength of Evzio and how those exposures intersect with naloxone dosing recommendations, including those for the pediatric population.

2. Background

Accidental or intentional overdose and death associated with the use, misuse, and abuse of illicit and/or prescription opioids is a public health crisis in the United States. Opioid overdose can occur in a patient prescribed an opioid medication or in household contacts of the patient and in people who misuse or abuse opioids. Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that, if not immediately treated, may lead to significant morbidity and mortality due to irreversible hypoxic injury. Naloxone is a nonselective opioid receptor antagonist, with the greatest affinity for the mu-opioid receptor that, if immediately administered, can reverse these life-threatening effects in an opioid overdose and prevent hypoxia-associated injury and death. However, there are limitations to the use of naloxone in this setting. The effects of some opioids, such as buprenorphine, may be difficult to antagonize. Larger doses of antagonist may be necessary than are available and the opioid overdose must be reversed before hypoxia results in irreversible injury. Also, it is important to realize that the duration of antagonists such as naloxone are generally shorter than the duration of action of most opioids. Therefore, even when an antagonist is available, it is not a substitute for seeking emergency medical help.

Expanded access to naloxone in the community is one component of the Commissioner's Opioids Action Plan which outlines FDA's plan for addressing the epidemic of opioid abuse, addiction, and overdose.¹ Evzio is currently approved as an injectable naloxone product that delivers 0.4 mg of naloxone hydrochloride intramuscularly or subcutaneously and is intended for use in the community. Narcan (naloxone hydrochloride) nasal spray is another drug-device combination product intended for use in the community and was approved on November 18, 2015. It delivers 4 mg (40 mg/ml) of naloxone intranasally and was the first intranasal product approved in this setting.

Generic versions of Narcan are currently available; the approved Narcan labeling recommends initial doses of 0.4 mg to 2 mg for known or suspected opioid overdose in adults with repeat doses every two to three minutes up to a total of 10 mg. In children, initial doses of 0.01 mg/kg

¹ <http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm>

with repeat doses of 0.1 mg/kg are recommended. In neonates, the recommended initial dose is the same as what is recommended in other pediatric age groups (i.e., 0.01 mg/kg); however, the recommended repeat dose remains at 0.01 mg/kg. In contrast, the American Academy of Pediatrics (AAP) currently recommends an initial dose of 0.1 mg/kg for children ≤ 20 kg or ≤ 5 years of age. A fixed dose of 2 mg is recommended in children >20 kg or >5 years of age. The initial dose may be repeated at two to three minute intervals, as needed. The AAP recommendations often result in a higher initial dose than the lower end of the initial recommended dose range for adults. The AAP's recommendations have been incorporated into a variety of published pediatric drug references (e.g., Harriet Lane Handbook and others).

Naloxone has also been increasingly available in the community through a variety of public health programs, which have generally supplied an injectable formulation of naloxone (i.e., either a vial or syringe) along with a needle or mucosal atomizer device (MAD) to provide access to this life-saving medicine. The MAD allows for the injectable formulation to be delivered as an intranasal spray, typically from an injectable solution containing 2 mg of naloxone HCl in 2 ml of solution (off-label route of administration for this product). The bioavailability of this off-label intranasal route of administration using an MAD may be less than the exposure following approved routes of administration for naloxone, based on reports in the literature, but there are also reports in the literature and from addiction treatment programs that naloxone administered this way has been successful in reversing opioid overdose. Therefore, the minimum effective dose of naloxone is unclear.

Evaluating the efficacy of a new formulation or route of administration of naloxone to establish an effective dose range presents significant logistical and ethical challenges, as already-approved naloxone-containing products are available for treatment of this life-threatening condition, which, if not immediately treated, could result in substantial morbidity and mortality. The Division has determined that it would not be ethical to deliver an experimental naloxone to an actual patient suffering from opioid overdose and potentially delay life-saving treatment with an already-approved naloxone product in the context of a clinical efficacy study. Furthermore, intentionally administering enough opioid to actually create a clinically meaningful opioid overdose is not ethical.

Therefore, the Division has outlined a path for the clinical development of novel naloxone products, including those intended to be used in the community, which consists of demonstrating comparable or greater systemic exposure to naloxone with the new naloxone product, particularly in the early critical period after drug administration, as that achieved with an approved injectable naloxone product (i.e., Narcan 0.4 mg given intramuscularly). This relative bioavailability study would be conducted in healthy volunteers, thus obviating the need to conduct a study in patients suffering from an opioid overdose. This is the standard upon which the 0.4 mg strength of Evzio was approved.

A pre-sNDA meeting was held in December 2014, where broad agreement was reached on the pharmacokinetic (PK) data that will be required to support this application and that additional nonclinical data will not be required provided that local tolerability is assessed in the context of the PK study.

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