

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205787Orig1s000

SUMMARY REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

Summary Review for Regulatory Action

Date	April 3, 2014
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	205787
Applicant Name	Kaleo, Inc.
Date of Submission	December 20, 2013
PDUFA Goal Date	June 20, 2014
Proprietary Name / Established (USAN) Name	Evzio Naloxone HCl injection
Dosage Forms / Strength	0.4 mg/0.4 mL
Proposed Indication	• 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. • Evzio is intended for immediate administration as emergency therapy in settings where opioids may be present. • Evzio is not a substitute for emergency medical care.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL	Sharon Hertz, MD
Medical Officer Review	Steven Galati, MD, Josh Lloyd, MD
Pharmacology Toxicology Review	Carlic Huynh, PhD, R. Daniel Mellon, PhD
CMC Review/OBP Review	Ying Wang, PhD, Julia Pinto, PhD, Prasa Peri, PhD
ONDQA Microbiology Review	Jessica Cole, PhD, Bryan Riley, PhD
Clinical Pharmacology Review	Wei Qiu, PhD, Yun Xu, PhD
CDRH REGODB/DMQ/OC GHDB/ DAGID/ODE ODE/DAGRID	M. Isabel Tejero del Rio, MD, PhD; Carl Fischer, PhD Lana Shiu, M.D., Keith Marin, QuynhNhu Nguyen, Ron Kaye
OSI DBGC	Chase Bourke, PhD, Charles Bonapace, PharmD, William Taylor, PhD
OC/OMPQ	Juandria Williams
OSE/DMEPA	Vicky Borders-Hemphill, PharmD, Morgan Walker, PharmD, Kellie Taylor, PharmD, MPH. Irene Chan, PharmD, BCPS
OND/SEALD	Abimbola Adebawale, Eric Brodsky, MD
OPDP/DCDP	L. Sheneé Toombs, Olga Salis, Michale Wade
OMP/DMPP	Karen Dowdy, RN, BSN, Sharon Mills, BSN, RN, CCRP, L. Sheneé' Toombs, PharmD, Barbara Fuller, RN, MSN, CWOCN, LaShawn Griffiths, MSHS-PH, BSN, RN
Pediatric and Maternal Health Staff Review	Erica Wynn, MD, MPH, Hari Sachs, MD, Lynne Yao, MD.

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Errors Prevention
 OPDP=Office of Prescription Drug Promotion
 DCDP=Division of Consumer Drug Promotion
 OMP=Office of Medical Policy Initiatives
 DMPP=Division of Medical Policy Programs
 OSI=Office of Scientific Investigations
 CDTL=Cross Discipline Team Leader
 ONDQA=Office of New Drug Quality Assessment
 OC=Office of Compliance
 OMPQ=Office of Manufacturing and Product Quality

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1. Introduction

The Applicant has submitted this NDA in support of marketing approval for Evzio, their naloxone autoinjector designed for use in nonmedical settings to reverse opioid overdose due to either accidental or intentional overdose. Evzio is a single-injection, fixed-dose, (b) (4) autoinjector that is designed to deliver 0.4 mg of naloxone HCl intramuscularly or subcutaneously. The unit incorporates both audio and visual instructions and cues to guide the person administering the drug during a medical emergency and is appropriate for administration by non-medically trained individuals. This application was submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and references NDA 016636 for the approved product Narcan.

2. Background

Naloxone was first approved in 1971 to reverse opioid intoxication or overdose. It is widely used both by hospital and first responder personnel. With the increasing medical use of opioid analgesics, and the increasing misuse and abuse of these drugs, there has been a marked increase in opioid overdose in both the pain patient and addiction patient populations. As it is frequently successful in reversing even severe opioid overdoses, naloxone has been increasingly used by non-health care professionals, including family, friends and other caregivers. A number of jurisdictions across the US have begun providing naloxone to patients, and providing instruction for its use to the patients' family, friends and/or caregivers. However, as the products are only available in glass vials and ampules, they are distributed with syringes and needles for manual injection, or with syringes and atomizers for nasal administration. Nasal administration is an unapproved route which could require higher doses than the approved routes if the bioavailability is different. These "kits" can be lifesaving, but they are more difficult to use than an autoinjector for most lay people. The addition of this easy to use product, with little to no associated risk, would be of potentially great public health importance.

Given the fact that it would be infeasible to perform a clinical efficacy study, and given the vast clinical experience with naloxone, the Division of Anesthesia, Analgesia, and Addiction Products agreed that the evidentiary basis for efficacy and safety could be the submission of a single, pivotal bioequivalence study that demonstrated comparable pharmacokinetics between the novel formulation and a generic naloxone product, (as the NDA product is no longer marketed), delivered by an approved route of administration. The Applicant has submitted such a study, and the review team has determined that it does, indeed, demonstrate bioequivalence between the products. In addition, the Agency required the evaluation of the safety and efficacy of the device, and a human factors validation

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study, both of which were completed by the Applicant and submitted with the NDA. The results of those studies are discussed below.

3. CMC

The following has been reproduced from pages 4 through 10 of Dr. Hertz's review:

Dr. Ying Wang performed the review of the drug substance and drug product. The information for the drug substance is referenced in DMF (b) (4) for which (b) (4) is the holder. According to Dr. Wang, the drug substance specifications mostly follow the USP and EP monographs and additional specifications for related substance meet the criteria in the ICH Q3A guideline. The drug product constituent component, 0.4 mg naloxone hydrochloride in an (b) (4) filled into a Type I (b) (4) glass cartridge (i.e., primary container closure), has the same formulation as a listed drug product (International Medicinal Systems, Naloxone HCl Injection, USP [1 mg/mL]. The only excipients are sodium hydrochloride, hydrochloric acid, and water. The drug product batches for the clinical study and registration stability lots meet the specifications.

The container closure system include the glass cartridge, a Type I (b) (4) gray (b) (4) rubber plunger which has contact with the drug solution, and an aluminum-crimping cap which does not have contact with the drug solution. The materials in contact with the drug solution comply with the USP and European Pharmacopoeia and are suitable for the storage of sterile drug product solution. An extractables study was completed with the rubber plungers and seals using a placebo of the drug product solution placebo (NaCl, pH 3.4) and isopropanol, as a control solvent. No significant peaks from the plunger or seals were observed.

The drug product was stable during stability testing with relatively low impurity levels. The Applicant submitted 12 months of stability data under term storage conditions (25°C/60% RH), 6 months under intermediate storage conditions (30°C/65% RH), and 6 month accelerated storage condition (40°C/75% RH) are provided in the submission. The stability data support the proposed expiry of the earlier of either 27 months from the manufacturing date for the drug constituent component of EVZIO or 24 months from the date of final assembly, packaging, and labeling of EVZIO.

The drug constituent component manufacturing sites were all found to be acceptable by the CDER Office of Compliance.

The Applicant was granted a categorical exclusion for the environmental assessment based on the rationale that there would be a very low estimated concentration of drug substance at point of entry into the aquatic environment.

Dr. Jessica Cole conducted the product quality microbiology review. The drug is (b) (4) and filled into a glass cartridge. The filled glass cartridge is assembled with the needle and protective sheath. This cartridge assembly is (b) (4). Dr. Cole found the response to requested information adequate and the Applicant agreed to a request amendment to the specification for endotoxin to (b) (4) EU/mg naloxone to prevent potential pyrogenic reactions in infants.

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The CDRH engineering review was conducted by Lana Shiu, MD. The device is a user-operated, (b) (4), needle-based system with audible and visual cues to guide the user through administration once the device is removed from its outer case. The Drug Cartridge container closure system for the naloxone drug product consists of a Type 1 (b) (4) glass Cartridge with an (b) (4) Plunger and an aluminum Crimp Cap lined with an (b) (4). When activated, the device injects a single dose of 0.4 mL (0.4 mg of naloxone HCl).



The total needle length is 5/8 of an inch and 1/4 of an inch extends outside the device upon actuation. The needle is fully retracted into the device housing after use. (b) (4). (b) (4) make contact with the drug product or injection site at any time.

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(b) (4)

(b) (4)

As noted by Dr. Shiu (p. 4):

Under dosing is prevented (b) (4)

The Volume Dispensed is defined as a release specification to ensure dosing accuracy.

In addition, (b) (4). The activation, needle penetration, drug injection and retraction of the needle occur in less than five seconds, and of that time, the actual needle penetration and drug injection time is (b) (4). A red safety guard prevents accidental activation of the injection.

Also noted by Dr. Shiu (p.6):

(b) (4)

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Intelliject (device developer for both NAI and EAI) relied on the prior validation study of EAI to support NAI development plan. CDRH provided the engineering device consult on the autoinjector and its software during the review of EAI (epiCard) during the IND 76367 as well as during the NDA 201739.

Device design, materials of construction, biocompatibility, sterilization, and shelf-life expectancy are consistent with that of IND 76367/NDA201739.

Per FDA's 2005 Guidance: *Medical Devices with Sharps Injury Prevention Features*, 500 NAI devices were tested *in-vitro* to confirm needle retraction. All 500 devices passed needle retraction testing, further verifying the NAI retractable needle feature as described in report IJ-731R-03O.

Dr. Shiu concluded that safety and efficacy have been demonstrated in this device.

The CDRH Human Factors and Device Use review was conducted by Ms. Quynh Nhu Nguyen. Preliminary and formative studies were conducted to optimize labeling, instructions for use and device design user interface. A human factors validation study was conducted with 40 participants, consisting of 19 juveniles and 21 adults, asked to deliver a simulated injection without training. Ms. Nguyen noted the following (p. 4):

The following sections provide a discussion on the observed use errors and difficulties which included the four issues identified above:

- Five juvenile participants used the trainer instead of study device but post-test user interview showed that these participants confirmed that they knew which device was which, and stated that they used the trainer intentionally because the simulation as a test or pretend situation.
- Four juvenile participants experienced difficulty with pulling off red safety guard. Intelliject confirmed that all adult participants could remove the red safety guard, and four juvenile participants experienced some difficulty initially but were able to pull it off.
- Four adult participants and two juvenile participants did not inject into the outer thigh but instead, they injected into the front or back of the thigh, inner thigh, etc. Intelliject confirmed that NAI is indicated for subcutaneous or intramuscular administration. While Intelliject has determined that the outer thigh is the ideal injection site location, if NAI were to be administered into the thigh, legs or upper arms/shoulder, they stated that the patient would still receive a SC or IM injection.
- Two participants (one adult and one juvenile) did not press device firmly against the skin for device activation. Based on post-test interview responses, Intelliject considered changes to the voice script to emphasize the need to push harder, and to wait until a click is heard. However, Intelliject believes that if a user commits a critical use error, the residual risk is that the

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patient would be receiving the current standard of care from paramedic and EMT personnel.

- Two juvenile participants did not hold the device in place for at least 1 second. Intelliject confirmed that the injection time of the needle and dispensing time of the drug is less than (b) (4). In addition, the voice prompt provides a device count down “five, four, three, two, one” after the injection is initiated.

Ms. Nguyen concluded that the results of the human factors study were acceptable, and no further optimization on the design and/or labeling was necessary.

The CDRH Office of Compliance review was conducted by Dr. Isabel Tejero del Rio. A number of deficiencies were identified and submitted to the Applicant following her initial review dated January 21, 2014. In a memo dated February 18, 2014, Dr. Tejero noted that the Applicant’s response to the deficiency letter dated January 22, 2014, was adequate with no residual deficiencies. Two facilities were identified as being subject to applicable Medical Device Regulations under 21 CFR Part 820. One site, Kaléo Inc., had an inspection on June 27, 2011, that was classified no action indicated (NAI). The second site, (b) (4)

Therefore, although an inspection under the Medical Device regulation on (b) (4), was classified NAI, a recommendation was made for a pre-approval inspection for compliance with 21 CFR Part 820. Dr. Tejero did note the following (p. 4):

However, CDRH/OC would consider acceptable a post-market inspection of the (b) (4) facility due to the public health benefit of the rapid approval of Evzio naloxone autoinjector, and based on the adequate desk review and previous NAI inspections of two (b) (4)

A form FDA-483 was issued for the (b) (4) site with three observations. The first observation was that the firm was (b) (4)

The Applicant responded that they were awaiting the final labeling from FDA prior to completing (b) (4). The required documentation to complete a desk review of the (b) (4) assembly line and investigators were able to observe the line in action and found no deficiencies.

The next two observations were:

OBSERVATION 2: Process control procedures that describe any process controls necessary to ensure conformance to specifications have not been adequately established. Specifically:

- A. The firm is not currently (b) (4) in that they have not completed the performance qualification for (b) (4)

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(b) (4)

Qualification of the controlled environment areas is required before the firm may proceed with the commercial scale process performance qualification (PPQ) batches.

B. The equipment qualification protocol, (b) (4)

Evaluation: The investigator stated during the March 21st call that the firm (b) (4)

The investigator indicated that she did not have any major concerns respect to the qualification process. Furthermore, the investigator believed that (b) (4) could be completed within a week, as indicated by the firm.

OBSERVATION 3: Procedures for corrective and preventive action have not been adequately established. Specifically,

(b) (4)

Evaluation: the investigator stated during the phone call of March 21st that this observation had been corrected before they closed the inspection. Thus, CDRH/OC has no additional concerns regarding the issue.

Dr. Tejero concluded that, based on the nature of the observations cited in form FDA-483, in conjunction with discussions with the investigators, district office, the CDER Office of Compliance and the CDRH Office of Compliance, the inspection was classified Voluntary Action Indicated and that in conjunction with a satisfactory desk review of the NDA, adequate inspectional history of (b) (4) and the VAI classification for the inspection results of (b) (4), the application could be approved.

I concur with the conclusions reached by the chemistry reviewer and the CDRH reviewers regarding the acceptability of the manufacturing of the drug product, drug substance, and drug-device combination. Manufacturing site inspections were acceptable. Stability testing supports an expiry of the earlier date of either 27 months from the manufacturing date for the drug constituent component of Evzio or 24 months from the date of final assembly, packaging and labeling of Evzio. There are no outstanding issues.

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I concur with the review team that there are no outstanding CMC concerns that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

The following has been reproduced from page 10 of Dr. Hertz's review:

No new nonclinical studies were submitted in support of this application. There were no novel excipients and the specifications proposed for the drug substance impurities and drug product degradants all meet ICH Q3A(R2) and Q3B(R2) qualifications thresholds. There were no concerns based on the results of the extractable and leachable study. Recommendations for the product labeling were incorporated into the package insert, including the recommendation for Pregnancy Category B. As noted by Dr. Huynh, there is some inconsistency with the pregnancy category in package inserts for naloxone products, with some changed from Category B to C after 2001, without a rationale stated in reviews at the time. Dr. Huynh and his supervisor, Dr. Mellon, conclude that the change in category may reflect an error, and that available data suggest that Pregnancy Category B is more appropriate.

I concur with the review team that there are no outstanding pharmacology or toxicology issues that would preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the clinical pharmacology and biopharmaceutics data submitted in this application has been reproduced from pages 10 and 11 of Dr. Hertz's review:

Dr. Wei Qiu conducted the clinical pharmacology review. The Applicant conducted a randomized, 2-period cross-over study (Study IJ-900DV-030) in 30 healthy subjects of a single injection of 0.4 mg naloxone HCl for injection administered using EVZIO NAI or the reference naloxone HCl using a standard syringe into the mid-anterolateral thigh. The Injection was either subcutaneous intramuscular based on the depth of fat under the skin and overlying the muscle, and the needle length. The needle length for EVZIO NAI is a nominal 0.5 inch and the needle length for the reference was 5/8 inch. The naloxone plasma concentration-time profiles are shown in Figure 1 from Dr. Qiu's review (p. 9).

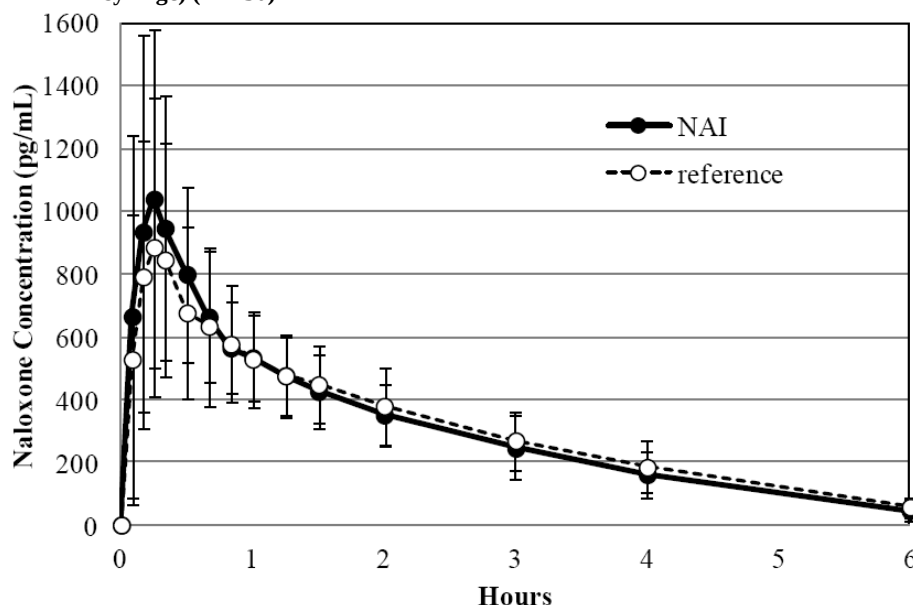
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Figure 1 Mean naloxone plasma concentration (ng/mL) time profiles following the administration of EVZIO NAI and Reference (0.4 mg injection via standard syringe) (N = 30)



The median T_{max} and half-life were similar for Evzio and the reference product (0.25 h vs. 0.33 h, and 1.28 h vs. 1.36 h). The AUC from the EVZIO injection was equivalent to the reference product (90% CIs of geometric mean ratios for naloxone AUC_t and AUC_{inf} within the bioequivalence limits of 80 to 125%). The C_{max} was 15% greater following EVZIO compared to the reference product (geometric mean 1.15, 90% CI [0.97, 1.37]).

Additional pertinent pharmacokinetic information is that following parenteral administration, naloxone hydrochloride is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation, and excreted in urine. Serum half-life in adults ranges from 30 to 81 minutes (mean 64 +/-12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 +/- 0.5 hours.

Inspections of the clinical and analytical portions of the comparative bioavailability study were conducted. No problems were identified and the data may be relied upon for Agency review.

I concur with the review team that there are no outstanding clinical pharmacology or biopharmaceutics concerns that would preclude approval of this application, and that the Applicant has provided data that demonstrate the bioequivalence of Evzio to naloxone.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

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7. Clinical/Statistical-Efficacy

No new efficacy data were submitted in support of this application.

8. Safety

The following summary of the clinical safety information submitted in this application has been reproduced from page 12 of Dr. Hertz's review:

There were no new safety studies submitted in support of this application. In the relative bioavailability study conducted in normal volunteers, dizziness, nausea, anosmia, dysgeusia, hyperhidrosis and hematoma were the only reported adverse event in subjects receiving Evzio. The comparator arm reported nausea, headache, injection site pain, and presyncope.

Naloxone is generally not administered outside of the setting of a suspected opioid overdose. Based on the adverse events reported in the labeling for Narcan, in the setting of an opioid-tolerant patient, administration of naloxone can result in precipitation of an acute withdrawal syndrome characterized by body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, and tachycardia. In the neonate, opioid withdrawal signs and symptoms also included: convulsions, excessive crying, and hyperactive reflexes.

Also as noted in the labeling for Narcan, in the postoperative setting, there have been post-marketing reports of hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation.

There is minimal to no risk from administration of a dose of 0.4 mg or 0.8 mg of naloxone to a person who has not had an opioid overdose if the person is not opioid tolerant. In the setting of a patient who is obtunded with respiratory depression, if the cause is not opioid overdose, no ill effect is expected, the instructions to seek emergency medical care are appropriate, and use of Evzio should not result in substantial delay in seeking that emergency care.

9. Advisory Committee Meeting

The application was not presented to an advisory committee as it is a simple reformulation of an approved drug that includes a new method of administration.

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10. Pediatrics

The following summary of the pediatric information in this application has been reproduced from pages 13 through 15 of Dr. Hertz's review:

Pediatric patients and children may be at risk for an opioid overdose as a result of several scenarios. Similar to adults, pediatric patients may receive an inadvertent overdose based on an error in dosing (too soon, too much), initiation of a concomitant drug that inhibits metabolism of the opioid, or cessation of a concomitant drug that had induced the metabolism of the opioid. In addition, children in a home where opioids are in use may come in contact with an opioid through improper storage or disposal, and become a patient in the setting of an overdose. Older children may experiment with opioid analgesics in an attempt to get high and inadvertently overdose. Therefore, pediatricians caring for pediatric patients prescribed opioids or caring for children who are otherwise well, but may be at risk for coming in contact with an opioid, may find it appropriate to prescribe naloxone for their patient or for children at risk for opioid contact, to be kept in the home as a safety precaution.

The package insert for Narcan includes pediatric labeling as follows:

USAGE IN CHILDREN

o Narcotic Overdose—Known or Suspected: The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone may be administered I.M. or S.C. in divided doses. If necessary, naloxone hydrochloride injection can be diluted with sterile water for injection.

This is in contrast to the following dosing regimen in adults:

USAGE IN ADULTS

o Narcotic Overdose—Known or Suspected: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of narcotic-induced or partial narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

The Applicant had discussed pursuing a waiver from pediatric studies under the Pediatric Research Equity Act based on there being only a small number of opioid overdoses in the pediatric population and a fixed-dose product was not suitable to accommodate weight-based dosing, that their product would not represent a meaningful benefit over currently approved products, and finally, that it was impossible or highly impracticable to conduct studies in pediatric patients.

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Regardless of the number of actual pediatric opioid overdoses, the number of children at risk is large based on the amount of opioid analgesics prescribed in the U.S., and the autoinjector configuration is intended to provide a benefit over the approved product that was only available in a vial for injection. However, not only are efficacy studies not feasible in pediatric patients in the same way they were not feasible in adults, even pharmacokinetic studies are not feasible because of limits regarding conducting studies in normal, healthy children. The Pediatric and Maternal Health Staff was contacted to assist with creating a path forward for pediatric populations. As noted in Dr. Wynn's review:

The following are off-label naloxone dosing recommendations, endorsed by the AAP [American Academy of Pediatrics] and the American Heart Association, for cardiopulmonary resuscitation and emergency cardiovascular care for full reversal of opioid effects:

- Younger than 5 years or body weight 20 kg or less: 0.1 mg/kg administered by IV push, intraosseous push, or by ET tube. Follow each dose given via ET tube with at least 5 mL of isotonic sodium chloride injection
- 5 years and older or body weight more than 20 kg: 2 mg administered by IV push, intraosseous push or by ET. Follow each dose given via ET with at least 5 mL of isotonic sodium chloride injection

However, weight-based dosing could result in a situation where it would be necessary to have multiple versions of the product on hand, and would risk a dose too low selected if an emergency arose.

Dr. Wynn expressed concern that the dose may be too low based on the recommendations of the AAP. However, limited data could be found in the Narcan application to support the pediatric dosing recommendations.

These questions were discussed further at a meeting of the Pediatric Research Committee on March 5, 2014. The dosing was considered adequate in the setting of use, the product was to be packaged with two doses so a second dose would be available, and as an initial treatment prior to the availability of emergency medical services. Another concern raised was that the needle could hit bone in the youngest patients as it was necessary to apply the autoinjector with some force. This could result in the needle breaking off or blockage of delivery of the drug. The Applicant cited the Center for Disease Control recommendation for a 7/8 inch needle for intramuscular vaccination in children ages 0 to 6 years, although this could result in over-penetration in 4% of children and the length of the exposed needle from Evzio is 0.5 inches. The following recommendations were made (from the meeting minutes dated March 20, 2014):

- The Division clarified that the intent of this product is to allow patients, caregivers, and guardians to administer this product when an intentional or unintentional opioid overdose is suspected. This product is being specifically developed to address the public health problems associated with widespread narcotic use/abuse.
- The PeRC discussed the risks of this product, which include failure to seek follow-up medical care, and breakage of the needle if it hits bone due to the needle length, and discussed whether the benefits outweigh the risks.

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- The PeRC concluded that it is reasonable to label the product now for all populations, but the Division should consider requiring the sponsor to conduct a safety study under FDAAA to ensure that the autoinjector can be used safely in the youngest population.
- The PeRC also recommended that labeling clearly describe safety concerns related to administration in small infants and children. The PeRC also agreed with the Division's plan to ensure that labeling clearly state that pediatric patients should seek medical care after administration of the product.

Language was added to the labeling with the instruction to pinch the thigh of pediatric patients less than one year of age to minimize the risk of striking bone. In addition, the Applicant agreed to commit to the following post-marketing safety requirement:

Conduct a study to demonstrate that the needle length is safe for use in patients less than one year of age during expected conditions of use.

11. Other Relevant Regulatory Issues

There were no unresolved regulatory issues associated with this application.

12. Labeling

The following comments regarding labeling have been reproduced from pages 15 and 16 of Dr. Hertz's review:

A proprietary name review by Dr. Borders-Hemphill found the proposed name Evzio acceptable.

Substantial changes were made to the package insert based on input from DMEPA, OPDP, SEALD, and DAAAP. While relying on the Agency's prior findings of safety and efficacy for Narcan, the Narcan package insert was not in the Physician Labeling Rule format, and contained language not consistent with current labeling efforts. First, the indication amended from language similar to Narcan as proposed by the Applicant:

(b) (4)

[Redacted text block]

The final agreed upon indication is based on the intended use of Evzio.

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.

EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present.

EVZIO is not a substitute for emergency medical care.

Key elements of this indication are that Evzio is for use of known or suspected opioid overdose. In the community, the reason for a patient appearing obtunded with respiratory depression is unknown. If opioid overdose is a possibility, Evzio should be administered. Therefore, it is important that Evzio be obtained by patients in advance of a problem, acknowledging that unplanned overdose can occur with the use of opioids. This will also allow patients and their immediate caregiver, family or friends to have time to become familiar with the instructions for use and the trainer. Also critical is the need to continue to pursue emergency medical care as the duration of effect of naloxone is frequently shorter than the duration of effect of opioids.

Evzio will be packaged with two active units and one trainer. This way, if the initial response is less than expected or if the initial response wanes prior to the availability of emergency medical help, another dose can be given.

Recommendations for the carton and immediate container labels from DMEPA were conveyed to the Applicant and implemented. The immediate container label was considered the labeling on the outer case and on the device itself. Requests for change from DMEPA for the active device and the trainer were implemented. In particular, the purpose statement, “(b) (4)” was proposed by the Applicant for placement in several areas on the active device labeling. The Applicant agreed with a request to change this statement to “for use in opioid emergencies such as overdose” to help minimize the risk of failing to identify an appropriate opportunity to use Evzio based on confusion between what constitutes an opioid emergency and an opioid overdose.

The patient labeling for Evzio consists of a patient package insert, instructions for use for the trainer and for the active device. Extensive revisions were requested from OPDP and DMPP that were conveyed to the Applicant and accepted.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant has provided substantial evidence that supports the safety, efficacy and product quality of their naloxone autoinjector product, Evzio. This will be the first approved naloxone product specifically designed for ease of administration by non-medical individuals in the setting of an emergency. It has minimal to no known risks and can potentially save numerous lives, including those of pain or addiction patients who accidentally overdose, and those of small children, teenagers and others inadvertently or intentionally exposed to opioids in settings where these drugs are not adequately secured. The potentially enormous benefits of this product clearly outweigh the minimal risks that may be associated with its use in reversing opioid overdose. A key risk associated with the use of Evzio is that there may be a failure to obtain adequate medical follow-up, which is critical following initial overdose reversal. That risk has been appropriately addressed to the best of the Applicant's ability by the inclusion of visual and audio instructions for the person administering the drug; these instructions include noting the need to obtain emergency medical care immediately after administration of the naloxone. Another important safety consideration is the risk of precipitating withdrawal in opioid-dependent individuals. However, the risk of death from an overdose clearly outweighs risks that may be associated with precipitated withdrawal. Furthermore, the product labeling describes the importance of understanding that only people experiencing respiratory depression along with excessive sleepiness should receive the product.

- Postmarketing Risk Management Activities

None

- Postmarketing Study Requirements

To address the risk of a needle striking bone in infants, the Applicant has agreed to the following postmarketing safety requirement:

Conduct a study to demonstrate that the needle length is safe for use in patients less than one year of age during expected conditions of use.

NDA 205787

Evzio

Division Director's Review and Summary Basis for Approval

April 3, 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
04/02/2014