

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209862Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

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.

3. CMC/Device

Pramoda Maturu, PhD, conducted the chemistry review, with secondary concurrence from Ramesh Raghavachari, PhD. Based on clarifying discussions with the chemistry review team, the drug cartridge will be manufactured at a (b) (4). Although the Applicant did not provide any stability data for product manufactured at that site, they provided 6 months of stability data generated on the same product that was manufactured at a (b) (4). The expiry recommendation is based on this supportive stability data from the (b) (4) site. The chemistry team recommends approval of this application with a 12-month expiry. The chemistry review team requested additional stability data during the review cycle to support a longer expiry. However, a response to that request has not been received at this time.

The CDER Office of Process and Facilities issued an overall manufacturing inspection recommendation of “Approve” on October 11, 2016.

There is a categorical exclusion for environmental assessment (CFR 25.31b) for this product.

Daniel J. Schu, PhD, conducted the product quality microbiology review, with secondary concurrence from Stephen E. Langille, PhD. Dr. Schu noted that “[b]ecause the applicant has proposed a change to the formulation of the drug constituent component of the combination drug-device product, the...microbiology review covers revalidation studies for (b) (4), the sterility test method and the bacterial endotoxins test method.” Dr. Schu found that “[t]he proposed change to the manufacturing process poses no additional risk to the microbiology quality of the subject drug product” and recommends this application for approval from the product quality microbiology perspective.

John McMichael conducted the Center for Devices and Radiological Health (CDRH) engineering review, with secondary concurrence from Alan Stevens. Although the device constituent is unchanged compared to the approved 0.4 mg Evzio product, the Applicant submitted data from functional performance testing and updated stability testing to confirm the essential performance requirements of the device with the higher concentration of naloxone. Over the course of the review, the CDRH reviewer noted that a design change was made to correct a dispensing time failure, but it appears that this change was made prior to the approval of the 0.4 mg Evzio product. Regardless, CDRH sent an information request to the Applicant to describe the design change and the subsequent qualification testing. The Applicant (b) (4)

Because the Applicant conducted stability testing post-design change and no failures were observed for any of the essential performance requirements of the combination product, including the exposed needle length, the CDRH reviewer found the response to be adequate.

As the Agency's approach to naloxone products intended for use in the community and the market continue to evolve, we now require Applicants of these products to provide certain types of data to establish the reliability of the drug-device combination product under a variety of conditions, given the life-threatening nature of the condition and the grave consequences associated with device failure. CDRH determined that this application does not contain adequate information regarding the reliability of the product. Although this information was not requested with the original application for Evzio, CDRH recommends requesting this information as a post-marketing requirement (PMR) at this time due to the importance of the information and its impact on the overall safety considerations for the product. This approach is consistent with that taken for naloxone products intended for use in the community.

The CDRH review team recommends approval for this application with PMRs for device reliability testing. The CDRH Office of Compliance recommendation for the device manufacturing facilities is pending at this time.

I concur with the conclusions reached by the product quality and device reviewers. There are no outstanding product quality or device issues that preclude approval.

Mónica Calderón, PharmD, BCPS, conducted the Division of Medication Error Prevention and Analysis (DMEPA) review, with secondary concurrence from Vicky Borders-Hemphill, PharmD, and Quynh Nhu Nguyen, MS. The Applicant submitted results from a labeling differentiation study to evaluate if participants can successfully differentiate between the 0.4 mg and the proposed 2 mg Evzio autoinjectors and cartons. The study consisted of 33 participants representing laypeople, pharmacists, and pharmacy technicians. DMEPA noted issues with the study to indicate that it was not a true label differentiation study. However, DMEPA focused their review on the information that the participants provided in terms of subjective feedback on what helped them in identifying the correct product, and DMEPA found the study results acceptable.

4. Nonclinical Pharmacology/Toxicology

Carlic K. Huynh, PhD, conducted the nonclinical pharmacology/toxicology review, with secondary concurrence from Elizabeth A. Bolan, PhD, and R. Daniel Mellon, PhD. No nonclinical studies were submitted with this application. Dr. Huynh noted that “[t]he drug substance and drug product specifications are identical to the approved 0.4 mg dosage strength product. The container closure is identical to the approved 0.4 mg dosage strength product, the extractable assessment was done appropriately with harsh solvents, and the leachable profile is not different than the currently approved drug product formulation. (b) (4) is present as a leachable; however, the levels do not represent a nonclinical safety concern.” The nonclinical pharmacology/toxicology team recommends approval from their perspective.

I concur with the conclusions reached by the nonclinical pharmacology/toxicology reviewer. There are no outstanding nonclinical pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Vincent (Peng) Duan, PhD, conducted the biopharmaceutics review, with secondary concurrence from Haritha Mandula, PhD. (b) (4)

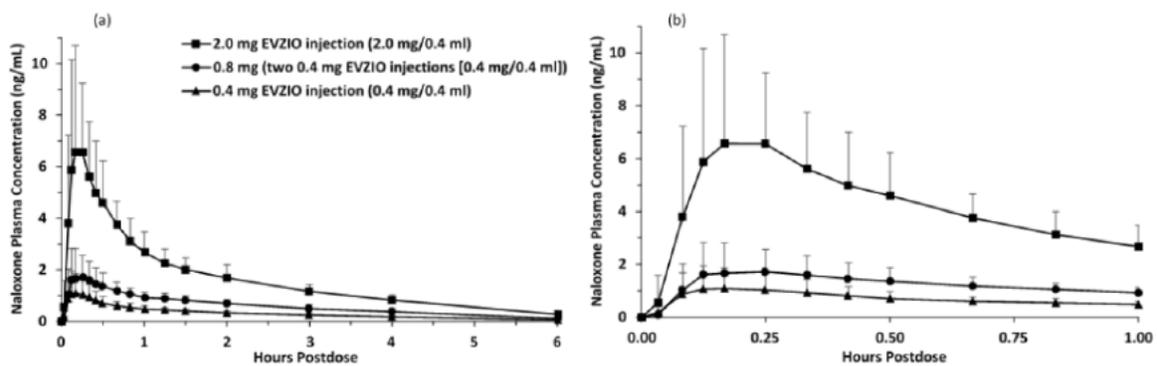
The Applicant previously conducted a bioavailability study to bridge the 0.4 mg strength to the reference product, Narcan. Dr. Duan noted that the bioavailability study the Applicant conducted in support of the current application demonstrated dose proportionality over the dose range of 0.4 mg to 2 mg and concluded that “the bridge...between the proposed drug product and the listed drug product has been established.” The biopharmaceutics review team recommends approval from their perspective.

Wei Qiu, PhD, conducted the clinical pharmacology review, with secondary concurrence from Yun Xu, PhD. According to the clinical pharmacology team, this application is acceptable. The following is a summary of the findings from the clinical pharmacology review.

The Applicant conducted study KA-900DV-05A (also referred to as study 05A, in this review), in support of this application. Study 05A was a randomized, six-sequence, three-period pharmacokinetic (PK) bioavailability and dose proportionality study that evaluated a single injection of Evzio 2 mg, a single injection of Evzio 0.4 mg, and two injections of Evzio 0.4 mg given 2 minutes apart in 24 healthy adult volunteers with a body mass index (BMI) between 18.5 and 32 kg/m², inclusive, and a weight of ≥50 kg and ≤100 kg. Study treatments were administered subcutaneously or intramuscularly to the mid-anterolateral aspect of the thigh and were given approximately 24 hours apart. All 24 subjects completed the study.

The mean naloxone plasma concentration time profiles are shown in Figure 1 below, and the pharmacokinetic parameters and statistical analysis of dose proportionality are shown in Table 1 below.

Figure 1. Mean Naloxone Plasma Concentration Time Profiles, (a) 0-6 h and (b) 0-1 h



Source: Dr. Qiu's review, pg. 3

Table 1. Summary of Naloxone Pharmacokinetic Parameters and Statistical Analysis of Dose Proportionality

Treatment	Statistic	C _{max} (pg/mL)	T _{max} (h)	T _{1/2} (h)	AUC _{0-t} (pg.h/mL)	AUC _{0-inf} (pg.h/mL)
Pharmacokinetic Parameters						
Reference (0.4 mg NAI)*	Mean (SD)	1328 (836)		1.58 (0.457)	1817 (290)	1995 (326)
	%CV	62.9		28.9	16.0	16.3
	Median (Min-Max)	980 (503-4220)	0.25 (0.09-0.84)	1.47 (1.05-2.76)	1864 (1322-2269)	1991 (1427-2688)
Test (0.8 mg naloxone HCl [two 0.4 mg NAIs])*	Mean (SD)	2156 (1021)		1.52 (0.360)	3498 (691)	3776 (720)
	%CV	47.4		23.7	19.8	19.1
	Median (Min-Max)	1855 (913-4160)	0.21 (0.09-0.85)	1.40 (1.11-2.39)	3435 (2334-5186)	3776 (2584-5438)
Test (2.0 mg NAI)	Mean (SD)	7905 (3617)		1.53 (0.382)	9657 (1488)	10330 (1565)
	%CV	45.8		25.0	15.4	15.2
	Median (Min-Max)	6950 (3020-14900)	0.25 (0.13-0.67)	1.47 (0.90-2.31)	9703 (6896-12760)	10410 (7420-13150)
Statistical Assessments of Dose Proportionality						
Dose normalized 2.0 mg / 0.4 mg†	GMR	1.24			1.06	1.05
	90% CI for ratio	1.04, 1.49			1.02, 1.11	1.01, 1.09
Dose normalized 0.8 mg / 0.4 mg	GMR	0.85			0.96	0.94
	90% CI for ratio	0.71, 1.02			0.92, 1.00	0.91, 0.98
Power Model (linear regression)	Slope	1.15			1.04	1.03
	95% CI	0.97, 1.33			0.98, 1.11	0.97, 1.09

Source: Dr. Qiu's review, pg. 3

A mean C_{max} of 7.90 ng/mL was reached at a median T_{max} of 15 min, with a mean half-life of 1.5 hours. The median T_{max} and mean half-life values were similar for the 2 mg and 0.4 mg doses of Evzio.

Dr. Qiu noted that “[d]ose proportionality for naloxone AUC_t and AUC_{inf} was demonstrated between 0.4 mg...and 2.0 mg...[However, n]aloxone C_{max} values were slightly greater than dose proportional for the same treatment comparison...[T]he naloxone concentrations at each time point after administration are much higher for the 2.0 mg [Evzio] than the 0.4 mg [Evzio].”

Dr. Qiu also noted that:

From clinical pharmacology perspective, [the] sponsor has adequately characterized the PK of the proposed new strength of [Evzio] (2 mg) and dose proportionality between 0.4 mg [Evzio] and 2 mg [Evzio]. According to the approved labeling for Narcan (naloxone HCl injection), the list[ed] drug product identified for [Evzio] in the original NDA submission, an initial dose of 0.4 to 2.0 mg is given IV (or via IM/SC administration if IV route is not available). In the original NDA, the 0.4 mg [Evzio] exhibited slightly (15%) greater C_{max} and equivalent AUC values [for] naloxone in comparison to the 0.4 mg naloxone HCl delivered via a standard syringe. The 2.0 mg [Evzio] showed about 5-fold AUC and C_{max} values compared

to the 0.4 mg [Evzio]; and the naloxone concentrations at each time point after administration are much higher for the 2.0 mg [Evzio] than the 0.4 mg [Evzio]. These PK results support the addition of the new strength for the indication of opioid overdose.

I concur with the conclusions reached by the clinical pharmacology and biopharmaceutics reviewers. There are no outstanding clinical pharmacology or biopharmaceutics issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No new clinical efficacy studies were submitted in support of this application. The Applicant is referencing the finding of safety and effectiveness for the reference product, Narcan (naloxone hydrochloride, NDA 16636), which is approved for known or suspected opioid overdose, to establish efficacy of the proposed product.

8. Safety

Elizabeth Kilgore, MD, conducted the clinical safety review with secondary concurrence from me. There were no new safety studies submitted in support of this application. However, the Applicant submitted the results of a pharmacokinetic study (study 05A), in which safety assessments were performed throughout the study, including evaluation of the injection site.

The Applicant is referencing the finding of safety and effectiveness for the reference product, Narcan (naloxone hydrochloride, NDA 16636), which is approved for known or suspected opioid overdose, to establish safety of the proposed product. The relative bioavailability study demonstrated that Evzio 2 mg achieves approximately 5-fold AUC and C_{max} values, as compared to Evzio 0.4 mg, which falls within the initial doses recommended in the approved Narcan labeling. Narcan labeling recommends repeat doses every two to three minutes up to a total dose of 10 mg.

Regarding the safety results from study 05A, Dr. Kilgore noted that:

There were no deaths, non-fatal serious adverse events (SAEs), or treatment-emergent AEs (TEAEs) that led to discontinuation from the study. Overall, 10 subjects experienced 15 TEAEs. The most frequently reported TEAE was mild erythema observed in all treatment groups and noted as localized erythema thought by the Applicant to be due to pressure markings from the device (10 events reported in seven subjects). Events of catheter site swelling, injection site bruising, dizziness, headache, and contact dermatitis were reported in one subject each. All TEAEs were

considered mild by the Investigator except for the event of headache that was considered moderate in intensity. The events of erythema, injection site bruising, and headache were considered by the Investigator to be possibly related or related to study drug. All events had an outcome of resolved. With the exception of erythema, no TEAEs occurred in more than one subject and no treatment-specific trends in TEAEs were noted among the three treatments. The number of subjects experiencing erythema was similar between the treatments, when taking into account that Treatment B [(two injections of 0.4 mg Evzio, given 2 minutes apart)] involved two injections.

There were no clinically significant safety laboratory values, vital signs, ECGs values, or physical examinations findings.

Dr. Kilgore concluded that “there were no new safety findings identified in this submission which would alter the known risk-benefit profile of naloxone.” I concur with Dr. Kilgore’s assessment.

9. Advisory Committee Meeting

An Advisory Committee (AC) meeting was not held to discuss this specific product. However, a general matters joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held to discuss naloxone products for community use.

The committees were asked to discuss naloxone products intended for use in the community, specifically the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages and the role of having multiple doses available in this setting. The committees were also asked to discuss the criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and the labeling to inform this decision, if multiple doses are available.

The following questions were asked of the committees:

1. **DISCUSS:** The current pharmacokinetic standard for approval of naloxone products for use in the community requires demonstration of naloxone levels comparable to or greater than the levels achieved with the approved starting dose of 0.4 mg of naloxone injection administered by one of the approved, labeled routes of administration in adults [intravenous (IV), intramuscular (IM), or subcutaneous injection (SQ)], with a minimum of two doses packaged together.
 - a. Discuss whether matching or exceeding the naloxone exposure from a 0.4 mg injection of naloxone represents a high enough naloxone exposure to remain the basis for approval of novel products. Please take into consideration the variety of opioids that may be involved in an overdose in the community

including: prescribed opioids vs. illicit opioids (heroin, heroin laced with fentanyl or carfentanil); partial agonists vs. full agonists.

- b. If you think a higher minimum naloxone level is more appropriate as the basis for approval of new products intended for use in the community, describe the target naloxone level and the rationale for this approach.
- c. In controlled settings with trained health care providers and adequate ventilatory support, naloxone can be titrated to reverse an opioid overdose and minimize the risk for precipitating an acute withdrawal syndrome in an opioid-tolerant individual. In the community, trained health care providers and adequate ventilatory support may not be available, and naloxone may be administered by a layperson relying solely on the instructions for use that accompanies the naloxone product. In this latter setting, there is a 5-to 10-minute window before hypoxic injury becomes irreversible. Discuss how to balance the need for rapid reversal of an opioid overdose with the risk for precipitating an acute opioid withdrawal syndrome when selecting the minimum naloxone exposure that forms the basis for approval of novel products.

2. **DISCUSS:** The approved dosing for known or suspected opioid overdose in adults is as follows: 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 opioid induced or partial opioid induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available. The approved dosing for known or suspected overdose in the pediatric population is as follows: The usual initial dose in pediatric patients 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. The past AAP recommendations for naloxone dosing in infants and children are as follows: 0.1 mg/kg for infants and children from birth to 5 years of age or 20 kg of body weight. Children older than 5 years of age or weighing more than 20 kg may be given 2.0 mg. These doses may be repeated as needed to maintain opiate reversal.

- a. Discuss whether the minimum exposure criterion (naloxone levels comparable to or greater than the levels achieved with 0.4 mg of naloxone injection) is appropriate for managing opioid overdose in children. If you do not think the standard is appropriate for children, discuss the criteria that should be used for naloxone products intended for use in children. Discuss whether the recommended criteria are suitable for use in adults.
- b. If different standards and resultant naloxone products are recommended for adults and children, one concern is that the presence of more than one naloxone product in a home may result in confusion about which product to administer in an emergency setting. Discuss how the risk of medication errors can be reduced in this setting.

- c. Discuss the need (if any) for PK and safety information in pediatric patients, depending on the route of administration and inactive ingredients, and any recommendations for how these data can be obtained.
3. **VOTE:** Is the pharmacokinetic standard based on 0.4 mg of naloxone given by an approved route (IV, IM, SQ) appropriate for approval of naloxone products for use in the community or are higher doses and/or exposures required?
 - a. Continue with the current minimum standard of comparable or greater exposure compared to 0.4 mg of naloxone injection
 - b. Increase the minimum acceptable naloxone exposure to that comparable to or greater than a higher dose of naloxone injection
4. **VOTE:** Should there be different minimum standards used to support the approval of products intended for use in adults and in children?
5. **DISCUSS:** Some Sponsors have proposed marketing more than one dose strength for their naloxone products intended for use in the community. When these strengths all meet or exceed the minimum naloxone exposure level set forth by the Agency, it is unclear what factors to describe in labeling to assist health care providers in making a decision to prescribe one dose strength over another.

Discuss what, if any, data Sponsors should provide to support the approval of more than one dose strength for any one naloxone product, and that can provide guidance to assist clinicians in dose selection.

6. **DISCUSS:** As part of the standard for approval, naloxone products intended for use in the community have Instructions for Use (IFU) suitable for use by laypersons as supported by human factors studies and additional training is not required.
 - a. Discuss whether there is a role for new naloxone products intended for use in the community that requires training beyond the IFU.
 - b. Discuss the characteristics that should be considered for the study population enrolled in human factor studies of novel naloxone products. In particular, discuss the appropriate age range of study participants and whether the studies should specifically enroll adolescents, and if so, down to what minimum age. Also discuss whether these studies should specifically enroll caregivers of infants and children.

In a community setting, where there is often lack of adequate supportive measures, including respiratory support, the risk of giving too low of a dose of naloxone is that overdose patients may die or develop irreversible hypoxic injury. In contrast, the risk of providing too much naloxone is precipitating opioid withdrawal symptoms.

The committees' discussion was largely split on the issue of whether the 0.4 mg standard is too low. Some members expressed the need to have a higher standard to ensure adequate reversal in this setting, due to the grave consequences associated with under treatment, while others felt that there were insufficient data to suggest that the 0.4 mg standard is not adequate. Many

members also expressed concern that withdrawal could be associated with a variety of behavioral manifestations, including violence, but noted that we do not have adequate data to suggest that a 2 mg standard would be too high.

When the question was taken to vote (Question 3), 13 members voted to keep the current minimum pharmacokinetic standard (i.e., 0.4 mg) and 15 members voted to increase the standard. Those in favor of increasing the standard felt that the availability of more potent opioids, including those that are illicit (e.g., street fentanyl and carfentanil), and extended-release/long-acting opioids is concerning and would require higher exposures to naloxone for adequate reversal. Those members felt that the benefit of utilizing higher exposures to save lives outweighed the risk of precipitating opioid withdrawal.

The committees also voted 21 to 7 to have the same standard in adults and pediatrics (Question 4). Some committee members also expressed concern that the 0.4 mg minimum standard is too low for the pediatric population and opined that weight-based dosing, as is recommended in the labeling for Narcan, is not appropriate for the community setting.

Although there was limited time available to discuss how to differentiate multiple doses in labeling, when available, some committee members noted a high potential for confusion among laypersons and favored not having multiple strengths available. Others noted that if the right dose is established that will work in the vast majority of adults and children, multiple doses are not necessary and it is an unnecessary exercise to try and describe different doses in labeling.

The committees did not have an opportunity to opine on Question 6.

10. Pediatrics

The Applicant received agreement on their pediatric study plan (PSP) for Evzio 2 mg on October 16, 2015.

Because Evzio 2 mg represents a change in dosing regimen (a fixed 2 mg dose) for naloxone, the Applicant is required to conduct a pediatric assessment under the Pediatric Research Equity Act (PREA). Efficacy studies are not feasible in pediatric patients in the same way they are not feasible in adults. However, unlike in adults, pediatric pharmacokinetic studies in healthy children are not feasible because of limits on the ability to conduct studies in normal, healthy children where the study involves more than minimal risk. Therefore, the Applicant was required to support the safety and efficacy of Evzio 2 mg in pediatrics, based on a review of available information, including the published literature, clinical practice guidelines, and the approved labeling for Narcan.

The Applicant submitted a pediatric assessment to support the efficacy and safety of the 2 mg dose in the entire pediatric age range, consistent with that described in the PSP, for which the Division of Pediatric and Maternal Health (DPMH) was consulted to review the adequacy of that assessment.

The DPMH review was conducted by Mona Khurana, MD, with secondary concurrence from John J. Alexander, MD, MPH.

Dr. Khurana concluded that:

The pediatric assessment supports the utility of the higher fixed naloxone dose provided by [Evzio 2 mg] to achieve and sustain opioid reversal, particularly in cases of pediatric exposure to long-acting opioids, large opioid ingestions, or both. The pediatric assessment also suggests that pediatric patients with acute opioid exposure may safely receive naloxone at cumulative doses of up to nearly 0.8 mg/kg. The assessment provides further evidence that precipitation of acute opioid withdrawal is unlikely to occur with use of [Evzio 2 mg] in the majority of the intended pediatric population since the most likely cause of opioid exposure in younger pediatric patients, particularly those less than 6 years of age, is acute accidental opioid ingestion. However, administration of the 2 mg fixed dose [of Evzio] in the subset of opioid-dependent pediatric patients, including neonates, may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome which can be life-threatening in neonates.

DPMH recommends approval of this application in the proposed indication in pediatric patients of all ages and provided pediatric labeling recommendations, including those to address the potential for precipitating acute opioid withdrawal in opioid-dependent pediatric patients.

This application was discussed at a meeting of the Pediatric Review Committee (PeRC) on September 21, 2016.

11. Other Relevant Regulatory Issues

Inspections

Inspections for the relative bioavailability study submitted in this application were not requested by the clinical pharmacology review team because inspections were completed during the review of the original NDA on the pivotal comparative bioavailability study that compared Evzio 0.4 mg to the reference product Narcan (study IJ-900DV-03O) and were found to be acceptable. The current application introduces a 2 mg strength for Evzio and its pharmacokinetic profile appears reasonable compared to the already-approved 0.4 mg strength of Evzio.

Financial disclosures

The Applicant certified that no financial arrangements with the clinical investigators were made that could affect the outcome of the study and no listed investigators were the recipients of significant payments of other sorts.

505(b)(2) Committee

This application was presented at a meeting of the 505(b)(2) committee on October 11, 2016, and it was cleared for action from their perspective.

12. Labeling

As noted by Dr. Lloyd:

“One of the concerns the Division has for the labeling of naloxone products intended for use in the community that have multiple doses available is regarding differentiating those doses in labeling to inform prescribers, and even laypersons, of the clinical scenarios or dosing criteria to determine when one dose would be used over another in a community setting, which is a different setting than was intended for the reference product Narcan. The Applicant’s submission did not include data to inform that decision. This issue was one of the points of discussion at the recently held Advisory Committee (AC) meeting, but due to time constraints, this issue was not fully explored at that meeting.

 (b) (4)
Therefore, the Division has decided to administratively split the applications for the 0.4 mg and 2 mg doses of Evzio into two NDAs (the application for the 2 mg product was initially submitted as a supplemental NDA to NDA 205787) and issue separate labeling for the 2 mg product upon approval.”

Dr. Calderon of DMEPA provided a consultation for the proposed FPI, IFU, container labels, and carton labeling and concluded that they are acceptable from a medication error perspective and that the differentiation study results are acceptable. Dr. Calderon noted, that “The subjective feedback from the study participants indicate that the participants utilized the new proposed color scheme to help differentiate between products in the label differentiation study.” Recommendations for labeling were conveyed to the Applicant and incorporated into the product labeling.

Dr. Walker of DMPP and Dr. Toombs of OPDP conducted a collaborative review of the labeling. Recommendations for labeling were conveyed to the Applicant and incorporated in the product labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval
- Risk Benefit Assessment

The Evzio 2 mg autoinjector delivers a dose of naloxone that results in naloxone levels proportionally larger than the original Evzio 0.4 mg autoinjector. The difference distinguishing the two products is that the concentration of the solution in the 2 mg autoinjector is 5 mg per mL, rather than 1 mg per mL as in the 0.4 mg autoinjector. The volume of solution, 0.4 mL, and the device are the same. FDA established the minimum naloxone exposure necessary for approving a new naloxone product for use in the community based on the dosing instructions for naloxone solution by intramuscular, intravenous, or subcutaneous injection, which calls for an initial dose of 0.4 mg to 2 mg, and repeated doses up to a maximum of 10 mg. The original Evzio 0.4 mg dose met this standard, (b) (4)

. The Evzio 2 mg dose can be expected to provide enough naloxone to reverse a large proportion of the individuals experiencing an opioid overdose, if not most, particularly as it is packaged with an available second dose.

The question of what represents the appropriate minimum naloxone levels for products intended for use in the community is a challenging one, given the extreme range of possible settings of opioid overdose. The complexity of this question is further emphasized by the advisory committee discussion from the October 5, 2016 meeting in which the risk of too low a dose versus the risk of too high a dose was discussed. The committee members voted 13 in favor of keeping the current standard of a naloxone dose that produces levels no less than the levels following administration of a 0.4 mg dose of injectable naloxone by IV, IM or SQ routes, and 15 voting in favor of raising the minimum. Members in favor of a higher standard expressed the importance of ensuring reversal of an opioid overdose from any opioid, regardless of potency. Those in favor of maintaining the existing standard expressed concern about possible behavioral manifestations from precipitating strong withdrawal symptoms, including agitation or violent behavior. Most committee members acknowledged the existence of gaps in our knowledge that makes these decisions difficult.

Another important question discussed at the meeting was whether it was possible to label a particular naloxone product intended for use in the community with more than one strength, given that there are no data to support when to use one strength over another. As discussed at the AC, the risk of creating confusion among prescribers or patients is a true concern and that a dose expected to be effective in the vast majority of overdoses in adults and children would preclude the need for multiple strengths of a product. (b) (4)

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

3135-1 Establish reliability requirements for the combination product EVZIO (naloxone hydrochloride injection) and complete testing that verifies combination product reliability.

The following recommendations pertain to the postmarketing requirement described above:

- a. Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as $R(t) = x\%$, where t = time and $x\%$ = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after pre-conditioning as described below. The reliability requirements should be verified with a high degree of statistical confidence.
- b. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.
- c. Describe the use conditions for the product.
- d. Define the functionality required for reliability.
- e. Define failure, as it relates to assessing the reliability requirements.
- f. Provide data to verify the reliability specifications. The acceptable endpoints for this data should be linked to your definition of failure.
- g. Devices assessed within the reliability data should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide a rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g. fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete.
 - Shipping
 - Aging
 - Storage orientation and conditions
 - Vibration handling
 - Shock handling (e.g., resistance to random impacts, such as being dropped)

- h. Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however you should provide rationale supporting the final circumstances of activation chosen.
- Activation orientation
 - Environmental temperature
 - Simulated injection through clothing (e.g., pants, jeans, etc.)
- i. Describe how manufacturing controls have been adequately implemented to achieve the reliability specification in the release product lots.

3135-2 Conduct case study analysis of reports of failure of the combination product EVZIO (naloxone hydrochloride injection) to activate, or failure of the combination product to deliver the full-labeled dose. Perform detailed analyses of reported device failures (including reported malfunctions that did, as well as did not result in patient harm). Reports should include a full narrative description of the failure, any subsequent adverse events, the results of root cause analysis performed for the reported failure, and a description of your procedures for monitoring and analyzing the reports.

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/s/

SHARON H HERTZ
10/19/2016