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MEDICAL REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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MEMORANDUM: PEDIATRIC REVIEW

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Through: John J. Alexander, M.D., M.P.H.
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To: Division of Anesthesia, Analgesia, and Addiction Products

Drug Name: 2 mg Evzio Auto-Injector

Active Ingredient: Naloxone Hydrochloride

Therapeutic Class: Opioid Antagonist

Subject: Review of Pediatric Assessment

Sponsor: Kaleo, Inc.

Materials Reviewed

- March 2014 DPMH Memorandum under NDA 205787 (DARRTS Reference ID 3480223)
- Approval History of Evzio 0.4 mg Auto-Injector (accessed at Drugs@FDA September 8, 2016)
- Regulatory History of NDA 205787/S-007 and under IND 112292 in DARRTS
- Reviewer's Guide, Module 1.9 (Pediatric Correspondence), and Module 2.5 (Clinical Overview) in sNDA 205787/S-007

Consult Request

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted DPMH to evaluate the adequacy of the sponsor's pediatric assessment in supporting approval of a proposed

2 milligram (mg) auto-injector dose in the full pediatric age range. DAAAP is also requesting DPMH provide pediatric labeling recommendations.

I. Background

A. Approval History of New Drug Application (NDA) 205787

Evzio 0.4 mg Auto-Injector (NAI) was approved on April 3, 2014 in all ages for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, and for immediate administration as emergency therapy in settings where opioids may be present.¹ This NDA was approved under the 505(b)(2) pathway on the basis of supportive data from the published literature and FDA's findings of safety and effectiveness for the previously approved Narcan for injection (NDA 016636).

Evzio is a single-injection, fixed-dose, auto-injector that is designed to deliver 0.4 mg of naloxone hydrochloride (HCl) intramuscularly (IM) or subcutaneously (SC) and was developed to facilitate administration of naloxone HCl by family members and caregivers (i.e., laypersons) in the non-healthcare setting. 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. The total needle length is 5/8 of an inch, and 1/2 of an inch extends outside the device upon actuation.² The needle is fully retracted into the device housing after use.

Pediatric considerations during the review of NDA 205787 included adequacy of the proposed fixed 0.4 mg IM or SC dose in pediatric patients of all ages and local safety of both routes of administration in the youngest pediatric patients. While noting that a 0.4 mg fixed initial dose may be too low to be effective in some patients or situations, DPMH nevertheless stated the overall efficacy of the 0.4 mg fixed dose has been established and cited the following additional reasons as to why additional dosing data are not needed prior to pediatric approval: (1) naloxone's wide safety margin in pediatric patients; (2) existing approved labeling supporting a dose of 0.01 mg/kilogram (kg); (3) the need for an easily administered naloxone device; and (4) the product was to be packaged with two doses so a second dose would be readily available prior to the arrival of emergency medical services (EMS).³ Given the public health need for this product, consensus was reached between DPMH, DAAAP, and the Pediatric Review Committee

¹ Approval Letter for NDA 205787

(http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/205787Orig1s000ltr.pdf; accessed September 8, 2016)

² April 1, 2014 Cross Discipline Team Leader Memorandum under NDA 205787 (DARRTS Reference ID 3481785).

³ March 2014 DPMH Memorandum under NDA 205787 (DARRTS Reference ID 3480223)

(PeRC) that the product should be labeled for all pediatric ages as long as potential safety concerns in the youngest pediatric patients are adequately addressed in product labeling and evaluated in a post-marketing safety study. The PeRC agreed that approving NAI for use in all pediatric populations was reasonable but raised concerns that, in the youngest patients, the needle could strike bone, break off, and/or potentially not deliver the intended dose of a potentially life-saving drug. The PeRC further expressed concern that adequate delivery could be further compromised if the soft tissues of the thigh are compressed while delivering the drug.

At the time of approval, no Pediatric Research Equity Act (PREA)-mandated post-marketing study requirements were issued, but the following post-marketing safety study requirement was issued under the Food and Drug Administration Amendments Act (FDAAA) of 2007:⁴

2140-1 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.

Final Report Submission: 10/29/2014

The study protocol for PMR 2140-1 was reviewed under Investigational New Drug (IND) 112292 in consultation with DPMH and found to be acceptable to fulfill the PMR and consistent with the Centers for Disease Control recommendations for needle injections. DAAAP and DPMH reviewed the final study report submitted to FDA on October 29, 2014 (Study IJ-735E-030: "NAI Needle Integrity Testing").^{5,6} In this study, the Evzio needle was injected into ham bone through a 4 inch skin pad to simulate injection into human bone. Twenty samples were tested at each of three locations (epiphysis, near the epiphyseal plate, and diaphysis), resulting in the testing of 60 total samples.

According to DAAAP's review of the study, results demonstrated that damage occurs to the needle when injected into bone, as manifested by bent needle shafts and needle tips, with the worst damage occurring when the injection occurs into compact bone (e.g. diaphysis, near epiphyseal plate). However, the needle appeared to remain intact and the drug was delivered in all samples tested. Two samples injected into epiphysis showed slightly delayed retraction times

⁴ April 2011 Guidance for Industry Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act:
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172001.pdf>;
accessed September 10, 2016.

⁵ July 7, 2015 DAAAP Medical Officer Review of PMR Study Report under NDA 205787 (DARRTS Reference ID 3788578).

⁶ January 26, 2015 DPMH Medical Officer Review of PMR Study report under NDA 205787 (DARRTS Reference ID 3690618).

of 5 seconds and 7 seconds, but DAAAP concluded the device continued to deliver naloxone in a reasonable timeframe even when retraction times were delayed. DAAAP noted that existing labeling language about pinching the thigh muscle in patients less than 1 year of age prior to Evzio administration should be retained to help reduce the likelihood of needle striking bone. DAAAP concluded that, although there were no instances of needle fragmentation, needle damage did occur and it would therefore be prudent to retain language in labeling that states the injection site should be inspected for residual needle parts, signs of infection, or both. DAAAP recommended continued routine post-marketing pharmacovigilance to monitor for adverse events related to any delays in drug delivery.

DPMH Comments: DPMH agrees with DAAAP's conclusion and recommendation to retain labeling language about inspecting the injection site for residual needle parts, signs of infection, or both.

DPMH did not recommend any additional labeling revisions based on the study results and did not recommend the need for any additional data to fulfil the PMR. Given the two reports of temporary drug flow restriction when bone impact blocked the needle opening, DPMH did recommend that DAAAP consider consulting the Center for Devices and Radiological Health if there are continued concerns about temporary drug flow restriction or if post-marketing adverse events related to delays in drug delivery are reported.

B. Regulatory History of Supplemental NDA 205787/S-007

The sponsor submitted a Prior Approval Supplement (PAS) on April 19, 2016 to seek approval of a new 2 mg strength Naloxone Auto-Injector (NAI-HD) for the same indications as currently approved for Evzio. The sNDA is supported by a pivotal dose proportionality study in 24 healthy adults, 24 to 54 years of age, comparing the 2 mg NAI-HD dose with the 0.4 mg Evzio dose. The sponsor also conducted a product label differentiation study in 33 participants to determine users' ability to visually identify and successfully differentiate between the 0.4 mg Evzio and the proposed 2 mg NAI-HD devices and cartons. FDA did not require additional human factors studies to evaluate device-related efficacy for NAI-HD.

NAI-HD is a drug-device combination product consisting of a single-use auto-injector which delivers a 2 mg naloxone dose via IM or SC injection. The formulation and dosing volume are identical to that of Evzio, but the NAI-HD product contains a higher naloxone HCl concentration (2 mg/0.4 milliliters [mL]) compared to Evzio (0.4 mg/0.4 mL). The needle specifications of the NAI and NAI-HD are identical. The exposed needle length for NAI-HD ranges from (b) (4) inches.⁷

⁷ Module 3.2.P.5 of NDA 205787/S-007 submission

At a pre-sNDA meeting, FDA advised the sponsor to submit a review and analysis of the published literature, leveraging existing pediatric information in approved labeling for their reference product, to evaluate the safety and effectiveness of the 2 mg dose of NAI-HD in all pediatric populations, similar to what the sponsor did to support pediatric labeling for Evzio 0.4 mg Auto-Injector.⁸ FDA recommended including these data with the sNDA submission. An Agreed Initial Pediatric Study Plan (iPSP) containing this information was included in the sNDA submission.⁹

The Agreed iPSP includes a tabular summary comparing naloxone exposure based on the fixed-dose administration of Evzio to NAI-HD in pediatric patients weighing 4.1 kg to 95.2 kg. See Appendix A. According to the sponsor, this information shows that administration of a fixed 2 mg dose via the NAI-HD is consistent with pediatric dosing recommended in approved naloxone HCl labeling and recommended by the American Academy of Pediatrics for all patients weighing more than 20 kg but is higher than both approved labeling and AAP dosing recommendations for patients weighing less than 20 kg. A 2 mg dose of NAI-HD will provide a 0.49 mg/kg naloxone dose to patients weighing 4.1 kg.

DPMH Comments: The sponsor's table does not account for pediatric patients down to birth and whose weight is more than two standard deviations from the mean for age. If the proposed product is approved for use in all pediatric ages from birth to less than 17 years, then administration of a fixed 2 mg dose would result in the delivery of approximately 1 mg/kg naloxone to a newborn at the 5th percentile for weight and 0.7 mg/kg naloxone to a newborn at the 95th percentile for weight.¹⁰ These doses are 7 to 10 times higher than the initial naloxone dose recommended by the American Academy of Pediatrics' (AAP) Committee on Drugs (COD).¹¹ The AAP COD recommends a parenteral naloxone dose of 0.1 mg/kg for pediatric patients from birth to age 5 years or 20 kg of body weight and a dose of 2 mg for pediatric patients older than age 5 years or weighing more than 20 kg. Administration of the fixed 2 mg dose to a 16 year old at the 5th and 95th percentiles for weight would result in the delivery of 0.04

⁸ December 23, 2014 Meeting Minutes for Type B Pre-sNDA Meeting under IND 112292 (DARRTS Reference ID 3677802)

⁹ Agreement Letter issued to the sponsor on October 16, 2015 under IND 112292 (DARRTS Reference ID 3834210)

¹⁰ Centers for Disease Control and Prevention Clinical Growth Charts for Children Birth to 24 Months: [http://www.cdc.gov/growthcharts/who_charts.htm#The WHO Growth Charts](http://www.cdc.gov/growthcharts/who_charts.htm#The%20WHO%20Growth%20Charts); accessed September 10, 2016.

¹¹ Committee on Drugs Naloxone Dosage and Route of Administration for Infants and Children: Addendum to Emergency Drug Doses for Infants and Children. *Pediatrics* 86(3): 484-485, 1990.

mg/kg and 0.02 mg/kg naloxone, respectively.¹² These doses are less than the AAP recommended initial naloxone doses but higher than approved pediatric doses in Narcan labeling.

II. Pediatric Assessment

To support pediatric approval of NAI-HD, the sponsor re-evaluated the literature with a focus on the safety of naloxone at doses greater than 0.1 mg/kg, at fixed doses greater than 0.4 mg per dose, or both in pediatric patients. The sponsor identified six publications consisting of the following: (1) two case reports of accidental opioid ingestion in pediatric patients;^{13,14} (2) a case series describing accidental buprenorphine exposure in pediatric patients;¹⁵ (3) a retrospective case review describing symptomatic accidental buprenorphine exposure in pediatric patients;¹⁶ (4) a review article on the management of opioid overdose;¹⁷ and (5) a randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of naloxone in asphyxiated newborns.¹⁸

One case report described a 2 year old boy weighing 12.5 kg who became apneic with central nervous system (CNS) depression after oral exposure to 50 mg of nor-methadone due to a pharmacy dispensing error.¹³ He immediately improved after receiving an initial IV naloxone dose of 0.008 mg/kg but had recurrent CNS depression 1 to 2 hours later, requiring additional IV naloxone at higher doses. Administration of each subsequent naloxone dose reversed his narcosis but, because he deteriorated each time 30 to 60 minutes post-dosing, he was placed on a naloxone infusion at 0.024 mg/kg/hour for 10.3 hours. He received a total of 0.56 mg/kg

¹² Centers for Disease Control and Prevention Clinical Growth Charts for Children 2 to 20 Years: http://www.cdc.gov/growthcharts/clinical_charts.htm; accessed September 10, 2016.

¹³ Gourlay GK and Coulthard K. The Role of Naloxone Infusions in the Treatment of Overdoses of Long Half-Life Narcotic Agonists: Application to Nor-Methadone. *British Journal of Clinical Pharmacology* 15: 269-272, 1983.

¹⁴ Romac D. Safety of Prolonged, High-Dose Infusion of Naloxone Hydrochloride for Severe Methadone Overdose. *Clinical Pharmacology* 5: 251-254, 1986.

¹⁵ Geib AG, Babu K, Ewald MB, et al. Adverse Effects in Children after Unintentional Buprenorphine Exposure. *Pediatrics* 118: 1746-1751, 2006.

¹⁶ Pedapati EV and Bateman ST. Toddlers Requiring Pediatric Intensive Care Unit Admission Following At-Home Exposure to Buprenorphine/Naloxone. *Pediatric Critical Care Medicine* 12(2): e102-e107, 2011.

¹⁷ Boyer EW. Management of Opioid Analgesic Overdose *New England journal of Medicine* 367(2): 146-155, 2012.

¹⁸ Chernick V, Manfreda J, De Booy V, et al. Clinical Trial of Naloxone in Birth Asphyxia. *Fetal and Neonatal Medicine Journal of Pediatrics* 113: 519-525, 1988.

naloxone over 28 hours. He recovered uneventfully without sequelae and was discharged 3 days after hospitalization. No naloxone-related adverse events were reported.

The other case report described a 13 year old girl who was found unconscious with labored breathing after ingesting approximately 200-300 mg methadone HCl.¹⁴ She received naloxone 0.4 mg IV by EMS with increased level of consciousness and increased respiratory rate, but required three additional doses of 0.4 mg IV naloxone on the way to the emergency room (ER) due to recurring episodes of unresponsiveness. Her blood methadone concentration in the ER was 0.9 mg/liter (L); a blood concentration of 1.6 mg/L has been reported to be lethal. She required 3 additional 0.4 mg IV naloxone boluses in the ER before admission. Due to persistent periods of apnea upon admission, she was started on a continuous naloxone infusion at an initial rate of 0.006 mg/kg/hour that was titrated up to a maximum rate of 0.018 mg/kg/hour. She required a continuous naloxone infusion for a total of 65.5 hours during which time she received a cumulative dose of 0.65 mg/kg. No naloxone-related adverse events were reported.

The case series described five children less than 2 years of age with accidental ingestion of combination tablets containing buprenorphine and naloxone.¹⁵ Four of the 5 children were treated with IV naloxone at weight-based doses; one child received close to the labeled initial dose of 0.01 mg/kg (0.016 mg/kg) while the other 3 children received close to the AAP recommended higher initial weight-based dose of 0.1 mg/kg (0.072 mg/kg, 0.08 mg/kg, and 0.1 mg/kg). All 4 children improved with administration of the naloxone dose but required more than one naloxone IV bolus dose due to recurrence of respiratory depression, CNS depression, or both. The child given the initial starting dose of 0.072 mg/kg subsequently required an IV infusion due to recurrent lethargy at a rate of 0.045 mg/kg/hour for 17 hours. All 4 children who received naloxone had reversal of their respiratory depression and recovered uneventfully. No naloxone-related adverse events were reported.

The retrospective case review aimed to determine the prevalence of symptomatic buprenorphine exposure requiring pediatric intensive care unit admission in pediatric patients less than 3 years of age at a single academic center from 2007 to 2009, the severity of the associated toxicity, and what clinical interventions were effective.¹⁶ Nine cases of opioid toxicity, most commonly presenting with drowsiness or lethargy, were identified involving single-agent exposure to the combination product buprenorphine/naloxone at the child's primary residence. In all 9 cases, an orange residual liquid or a partial pill suggestive of the sublingual formulation was found, suggesting the drug had dissolved in the child's mouth instead of being swallowed. The median (range) age was 22 months (10 months to 33 months). Six patients received IV or IM naloxone at a mean (range) dose of 0.07 mg/kg (0.03 mg/kg to 0.1 mg/kg); 2 patients received their 1st dose by EMS pre-hospital and 4 patients received their first dose in the ER. One patient received an initial IV dose of 0.09 mg/kg and was then placed on an IV infusion at 0.05 mg/kg/hour for 16 hours; the infusion was started because the initial IV bolus dose did not sufficiently reverse the

respiratory effects of opioid exposure. The AAP recommended naloxone dose of 0.1 mg/kg was used in 3 cases. In the other 6 cases, smaller doses were effective at reversing symptoms. Naloxone administration was associated with marked clinical improvement in all cases. No naloxone-related adverse events were reported.

The randomized, double-blind, placebo-controlled trial was conducted in 193 newborns with low one minute Apgar scores due to intrauterine asphyxia who received 0.4 mg/kg IM naloxone or normal saline.¹⁸ Naloxone administration did not have a significant effect on spontaneous respiratory frequency or heart rate up to 30 minutes after injection or at 24 hours of age. Increased muscle tone of the upper and lower extremities was associated with naloxone use, which the authors opined was not desirable in the context of inadequate oxygen delivery to vital organs. The authors concluded that naloxone has no readily apparent benefit in the resuscitation of the asphyxiated newborn.

DPMH Comments: This trial was conducted exclusively in asphyxiated newborns, and newborns whose mothers had been given an opioid analgesic within four hours of delivery were excluded. Therefore, the safety findings are not necessarily generalizable to the population for whom NAI-HD would be indicated.

Overall, these publications support concerns that a single, low initial naloxone dose may be inadequate to provide continuous antagonism of opioid effects in some settings and that repeated doses of naloxone are necessary to achieve and sustain opioid reversal in cases of exposure to long-acting opioids, large opioid ingestions, or both.

Rare cases of adverse reactions to high doses of naloxone have been described primarily in post-surgical adult patients that consist of hypertension, arrhythmias, cardiac arrest, and gastrointestinal disturbances and are currently captured in product labeling. None of the six publications included in this pediatric assessment described naloxone-related adverse events in pediatric patients at administered cumulative doses of up to nearly 0.8 mg/kg.

These publications provide further evidence that precipitation of acute opioid withdrawal is unlikely to occur with use of NAI-HD in 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.^{19,20} However, administration of the 2 mg fixed dose via the NAI-HD in opioid-dependent pediatric patients, including neonates, may result in an abrupt

¹⁹ Martin TC and Rocque M. Accidental and Non-Accidental Ingestion of Methadone and Buprenorphine in Childhood: A Single Center Experience, 1999-2009. *Current Drug Safety* 6: 12-16, 2011.

²⁰ Hayes BD, Klein-Schwartz W, and Doyon S. Toxicity of Buprenorphine Overdoses in Children. *Pediatrics* 121(4): e782-e786, 2008.

and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. Neonatal opioid withdrawal syndrome (NOWs), unlike opioid withdrawal syndrome in adults, may be life-threatening.

III. Conclusions

The pediatric assessment supports the utility of the higher fixed naloxone dose provided by NAI-HD 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 NAI-HD 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 via the NAI-HD 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.

The proposed 2 mg fixed dose may be most appropriate for use by lay people in the community and other non-medically supervised settings where the goal would be rapid reversal of opioid effects due to acute accidental or intentional ingestion with less concern about precipitating acute withdrawal symptoms. Such settings are likely to have limited to no other treatment alternatives available. Therefore, precipitation of acute withdrawal symptoms would be preferable to the potentially life-threatening consequences of prolonged respiratory depression and hypoxia due to opioid overdose.

Use of the NAI-HD is less desirable when careful dose-titration rather than fixed dose-administration is needed by healthcare professionals in certain supervised medical settings such as post-operative recovery rooms and delivery rooms to avoid the consequences of abrupt reversal of chronic opioid effects. In these settings where slower, incremental reversal of opioid effects are needed as an adjunct to assisted ventilation and other supportive resuscitative measures, use of a naloxone-containing product that can be titrated to effect and dosed according to weight rather than as a large, fixed dose may be preferable and should be recommended.

IV. Recommendations

DPMH recommends approval of NAI-HD for the proposed indications in pediatric patients of all ages. Product labeling should capture the following:

- Safety concerns about precipitating acute withdrawal if this product is used in pediatric patients with chronic opioid exposure
- Convey the importance of using other naloxone products which can be dosed by weight, rather than NAI-HD, in supervised healthcare settings when careful dose-titration is needed
- Consistently state product may be re-administered for recurrent respiratory depression, CNS depression, or both; the proposed labeling currently only includes respiratory depression

DPMH recommends the following labeling revisions (suggested text added in bold italics and suggested deletions as strikethrough):

1 INDICATIONS AND USAGE

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 ***in adults and pediatric patients.***

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.

2.2 Dosing Information

Dosing in Adults and Pediatric Patients over Age One ***Year***

Instruct patients or their caregivers to administer EVZIO according to the Instructions for Use, intramuscularly or subcutaneously.

Dosing in Pediatric Patients under Age One ***Year***

In pediatric patients under the age of one ***year***, the caregiver should pinch the thigh muscle while administering EVZIO. ***Carefully observe the administration site for*** (b) (4)

5.3 Precipitation of Severe Opioid Withdrawal

The use of EVZIO in patients who are opioid dependent may precipitate an acute abstinence syndrome (b) (4) characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or

vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. **Unlike opioid withdrawal in adults, opioid withdrawal in neonates** ~~In neonates, opioid withdrawal~~ **manifesting as seizures** may be life-threatening if not recognized and properly treated. **Other** ~~and may include the following~~ signs and symptoms **in neonates include:** convulsions, excessive crying and hyperactive reflexes. **Monitor patients for the development of the signs and symptoms of opioid withdrawal.**



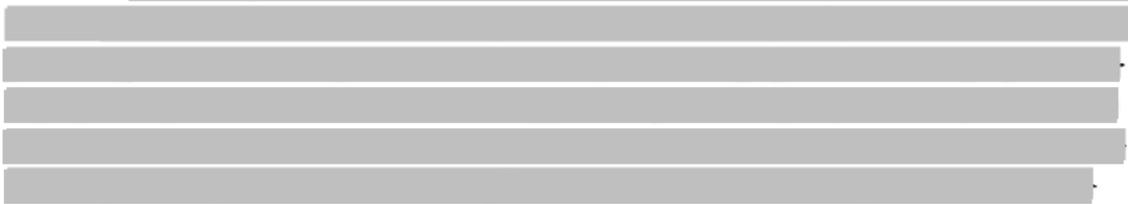
(b) (4)

8.4 Pediatric Use

The safety and effectiveness of EVZIO (for intramuscular and subcutaneous use) have been established in pediatric patients **of all ages** for [redacted] (b) (4)

[redacted] Use of naloxone hydrochloride in **all** pediatric patients is supported by [redacted] (b) (4)

[redacted] **No pediatric studies were conducted for EVZIO.** [redacted] (b) (4)



Absorption of naloxone hydrochloride following subcutaneous or intramuscular administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds [redacted] (b) (4) **appropriately** to naloxone hydrochloride injection, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.

In opioid-dependent pediatric patients, (including neonates), administration of naloxone **hydrochloride** may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. **There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. Unlike acute opioid withdrawal in adults, acute opioid withdrawal in neonates manifesting as seizures may be life-threatening if not recognized and properly treated. Other signs and symptoms in neonates may include excessive crying and hyperactive reflexes. In these settings where it may**

be preferable to avoid the abrupt precipitation of acute opioid withdrawal symptoms, consider use of an alternative, naloxone product which can be dosed according to weight and titrated to effect. [see Contraindications (5.3)].

In pediatric patients under the age of one year, the caregiver should pinch the thigh muscle while administering EVZIO. Carefully observe the administration site for evidence of residual needle parts, signs of infection, or both. [see Dosing Information (2.2)].

(b) (4)

(b) (4)

Appendix A

Naloxone Exposure Based on Fixed-Dose Administration of Evzio and NAI-HD

Weight (lbs)	Weight (kg)	EVZIO Dose (mg/kg)	2x EVZIO Dose (mg/kg)	05A Dose (mg/kg)	2x 05A Dose (mg/kg)
9	4.1	0.10	0.20	0.49	0.98
10	4.5	0.09	0.18	0.44	0.89
20	9.1	0.04	0.09	0.22	0.44
30	13.6	0.03	0.06	0.15	0.29
40	18.1	0.02	0.04	0.11	0.22
44.1	20	0.02	0.04	0.10	0.20
50	22.7	0.02	0.04	0.09	0.18
60	27.2	0.01	0.03	0.07	0.15
70	31.8	0.01	0.03	0.06	0.13
80	36.3	0.01	0.02	0.06	0.11
90	40.8	0.01	0.02	0.05	0.10
100	45.4	0.01	0.02	0.04	0.09
110	49.9	0.01	0.02	0.04	0.08
120	54.4	0.01	0.01	0.04	0.07
130	59	0.01	0.01	0.03	0.07
140	63.5	0.01	0.01	0.03	0.06
150	68	0.01	0.01	0.03	0.06
160	72.6	0.01	0.01	0.03	0.06
170	77.1	0.01	0.01	0.03	0.05
180	81.6	0.005	0.01	0.02	0.05
190	86.2	0.005	0.01	0.02	0.05
200	90.7	0.004	0.01	0.02	0.04
210	95.2	0.004	0.01	0.02	0.04

(Source: Table 2 on page 14 of Agreed iPSP included in Module 1.9 of sNDA 205787/S-007 submission)

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/s/

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09/22/2016

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Clinical Review
Elizabeth Kilgore, MD
NDA 205787
Evzio Naloxone Auto-Injector

CLINICAL REVIEW

Application Type Supplemental NDA
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Reviewer Name(s) Elizabeth Kilgore, MD
Review Completion Date September 16, 2016

Established Name Naloxone Injection
(Proposed) Trade Name Evzio
Therapeutic Class Opioid Antagonist
Applicant Kaleo, Inc.

Formulation(s) Injection
Dosing Regimen 2.0 mg single-dose
Indication(s) Opioid Overdose
Intended Population(s) Out-of-Hospital Treatment of
Opioid Overdose

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended pending resolution of how labeling should reflect the availability of two doses in the proposed setting, which will be the focus of an upcoming Advisory Committee (AC) meeting.

1.2 Risk Benefit Assessment

Injectable naloxone HCL 0.4 mg (Tradename Evzio) was approved via the 505(b)(2) pathway with the reference drug Narcan (NDA 016636) on April 3, 2014, under NDA 205787 for use in pediatric and adult patients of all ages to facilitate administration of naloxone hydrochloride (HCL) by family members, caregivers, and/or bystanders (i.e., laypersons) in the non-healthcare setting for reversal of opioid overdose. Each injection of Evzio delivers 0.4 mg naloxone hydrochloride injection (0.4 mL) in a pre-filled autoinjector (naloxone auto-injector [NAI]).

Approved Evzio is an opioid antagonist indicated for the following: 1) emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression; and 2) immediate administration as emergency therapy in settings where opioids may be present. Evzio is not a substitute for emergency medical care.

On April 19, 2016, Kaleo, Inc. (Sponsor/Applicant) submitted a supplemental New Drug Application (sNDA) to market a 2.0 mg dose of Evzio (2.0 mg/0.4 mL) Naloxone Auto-Injector [NAI]. The 2.0 mg dose is for the same indications as the currently approved 0.4 mg dose. This supplemental application was supported by establishing a PK and dose proportionality bridge between the approved Evzio 0.4 mg and the proposed dose of 2.0 mg in Study KA-900DV-05A, a randomized, single-dose, three-period crossover bioavailability, dose proportionality, safety, and tolerability study in 24 healthy subjects. The results of that study showed that the PK profiles for 0.4 mg NAI and 2.0 mg NAI were dose proportional for naloxone exposure. There were no deaths or non-fatal SAEs in the study population and no new clinically significant safety findings were noted when compared to the approved Evzio 0.4 mg.

The Applicant referenced the approved Evzio 0.4 mg label and literature to support the efficacy and safety of the 2.0 mg dose in the entire pediatric population, as was done for the 0.4 mg dose, according to an Agreed Pediatric Study Plan. The Division of Pediatric and Maternal Health (DPMH) was consulted to evaluate the Applicant's literature submitted to support labeling in the pediatric population. The DPMH consult response is pending at the time of this review. The Applicant's pediatric assessment is to be presented to the Agency's PeRC (Pediatric Review Committee) on September 21,

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2016. The outcome of the PeRC's recommendation is pending at the time of this review.

The Applicant's submission did not include data to inform prescribers or laypersons the clinical scenarios or provide clinical dosing criteria which would be employed to determine when the 0.4 mg dose should be used versus when the 2.0 mg dose should be used in a community setting, which is a different setting than was intended for the reference product. (b) (4)

We consider this to be potentially problematic and confusing for both prescribers and laypersons. Therefore, this issue, along with others, is to be discussed at a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to be held on October 5, 2016. The dosing information as currently written in the proposed label is shown below:

Proposed Label Dosing Information:

2.2 Dosing Information

Initial Dosing

Administer the initial dose of EVZIO to adult or pediatric patients intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary, and seek emergency medical assistance. Administer EVZIO as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death.

Repeat Dosing

The requirement for repeat doses of EVZIO depends upon the amount, type, and route of administration of the opioid being antagonized. If the patient responds to EVZIO and relapses back into respiratory depression before emergency assistance arrives, (b) (4)

If the desired response is not obtained after 2 or 3 minutes, (b) (4). If there is still no response and additional doses are available, administer additional doses of EVZIO every 2 to 3 minutes (b) (4) until emergency medical assistance arrives. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

In addition to a bioavailability study supporting the 0.4 mg dose, the initial Evzio 0.4 mg submission also included a comprehensive Human Factors program with regard to the device-related efficacy. Although no new summative human factors studies were required or conducted for the 2.0 mg NAI (as the design and user-interface are the same as the 0.4 mg NAI) there were two formative usability studies conducted after submission of the original NDA which were included in this supplemental NDA. Dr.

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Monica Calderon, Division of Medication Error Prevention and Analysis (DMEPA), reported that these two usability studies (IJ-1026SE-03O and IJ-1027SE-03O) were not formally reviewed by DMEPA because the studies did not use the 2.0 mg strength but involved a comparison of the 0.4 mg strength with an unapproved nasal naloxone delivery kit that used the injectable form of naloxone off-label. This supplemental NDA also included the results of the Applicant's product label differentiation study on the proposed 2.0 mg NAI devices and cartons. The Labeling Differentiation Study was reviewed by Dr. Calderon but the final review is pending at this time.

Naloxone is reserved mostly for use in the hospital setting for opioid overdose. In the outpatient setting, patients may intentionally or unintentionally overdose on opioids and require emergent treatment. This NAI product provides a mechanism for treatment of opioid overdose in the outpatient setting, to be administered by caregivers with or without medical training. Given these instances occur and are medical emergencies, a treatment option that is effective in this environment may have a substantial impact on patient safety from a public health perspective. The addition of a 2.0 mg dosage makes available the maximum recommended initial dose of naloxone.

In summary, NAI 2.0 mg is expected to provide the same life-saving benefits as other naloxone HCL products in the case of acute opioid-related toxicity, including suspected overdose. No new clinically significant safety issues were identified from those already known and included in the approved Evzio 0.4 mg label. Thus, the risk/benefit ratio is considered to be favorable for Evzio 2.0 mg NAI.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I have identified no further safety issues in review of this application that warrant additional postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements are recommended at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Naloxone is a narcotic antagonist, a synthetic congener of oxymorphone. The proposed 2.0 mg naloxone auto-injector (NAI) utilizes the same device constituent and dosing volume as approved Evzio 0.4 mg but a higher drug constituent at a higher concentration of naloxone HCL (i.e., 5 mg/mL for naloxone 2.0 mg rather than 1 mg/mL for naloxone 0.4 mg) to deliver 2.0 mg of naloxone versus 0.4 mg naloxone. Like

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approved Evzio 0.4 mg, the proposed 2.0 mg naloxone product is a single-use, NAI, combination drug-device product that delivers naloxone hydrochloride (HCl) via subcutaneous or intramuscular injection.

Evzio is intended for patients who receive opioids out-of-the hospital and develop acute, opioid-related, central nervous system or respiratory depression. Evzio is designed for a caregiver or layperson to administer naloxone in the out-of-hospital setting for the treatment of an opioid overdose.

The Applicant states that the Device Constituent Component of Evzio is a compact, user-actuated, (b) (4) auto-injector system that delivers 2.0 mg naloxone through a needle when activated.

The 2.0 mg dose is the recommended maximum initial dose of naloxone HCL given intravenously (IV) or intramuscular/subcutaneously if the IV route is not available as specified in the approved labeling for Narcan (naloxone HCL injection).

2.2 Tables of Currently Available Treatments for Proposed Indications

Narcan (naloxone) was originally approved in 1971 intended for administration in patients who suffered harm from an opioid overdose or suspected overdose. See further discussion under Section 2.3.

2.3 Availability of Proposed Active Ingredient in the United States

Multiple approved drug products containing the active ingredient naloxone are available and marketed in the United States (Table 1). Most of the approved products are combination products used for maintenance of opioid dependence. The naloxone component of the approved combination drug products is generally included to deter intravenous abuse.

Table 1. Availability of Naloxone Marketed in the U.S.

Drug Product Name	NDA	Approval Date	Dose Form	Indication
Narcan	016636	4/13/1971	Injection	Complete or partial reversal of opioid depression, including respiratory
Talwin NX (pentazocine/naloxone)	018733	12/06/1982	Tablet	Relief of moderate to severe pain
Suboxone (Buprenorphine/naloxone)	020733	10/08/2011	Tablet	Maintenance treatment of opioid dependence
Suboxone (Buprenorphine/naloxone)	022410	8/20/2010	Film	Maintenance treatment of opioid dependence
Zubsolv (Buprenorphine/naloxone)	204242	7/3/2013	Tablet	Maintenance treatment of opioid

Original submission, NDA 205787, Medical Officer (MO) review, p. 7.

2.4 Important Safety Issues With Consideration to Related Drugs

Naloxone may cause an abrupt and complete reversal of opioid effects leading to withdrawal symptoms (e.g., abdominal cramping, muscle aches, sweating, anxiety, nausea, vomiting, diarrhea). Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with use postoperatively and naloxone should be used with caution in patients with preexisting cardiac disease or who have received potentially cardiotoxic drugs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

NDA 205787, Evzio 0.4 mg was approved on April 3, 2014. See the NDA MO review for details regarding presubmission regulatory activity related to that submission.

For this supplemental NDA 2.0 mg, the major regulatory communication between the Division and the Sponsor was a pre-sNDA teleconference held on December 8, 2014 with a subsequent post-meeting email from the Sponsor to the Division. The key points from that meeting and email are summarized below:

- The Sponsor decided to seek approval of 2.0 mg NAI for all populations.
- We agreed with the Sponsor's proposal to conduct a 2-period, 2-treatment (Evzio 0.4 mg and NAI-HP 2.0 mg) crossover pharmacokinetic study in at least twelve subjects in each treatment group to support the safety and labeling for the 2.0 mg NAI and to establish dose proportionality.
- Although the Agency would normally require a nonclinical study to examine local tolerability as the proposed product represents a higher

concentration of naloxone, we informed the Sponsor that a clinical evaluation of local tolerability at the site of administration in the PK study would be acceptable.

- The Sponsor was informed that the proposed application will trigger PREA and the 2.0 mg dose may be appropriate as the initial dose in all pediatric patients as well. Therefore, they were advised to submit a review and analysis of the published literature, leveraging existing pediatric information in approved labeling for the reference product, to evaluate the safety and effectiveness of the 2.0 mg dose in all pediatric populations.

2.6 Other Relevant Background Information

There is no additional relevant background information. Refer to the original NDA submission MO review for background pertaining to the 0.4 mg NAI.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic submission contained the required data necessary to conduct the review.

3.2 Compliance with Good Clinical Practices

The Applicant reported that the key bioavailability study KA-900DV-05A was performed in compliance with Good Clinical Practice (GCP).

3.3 Financial Disclosures

The submission included Form 3454 (Financial Certification and Disclosure) for the six clinical investigators involved in the key bioavailability study KA-900DV-05A, in which the Applicant attested that no financial arrangements with the clinical investigators were made which could affect the outcome of the study as defined in 21 CFR 54.2(a) and no listed investigators were the recipients of significant payments of other sorts as defined in 21 CFR 54.2(f) as shown:

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

See Appendix 9.4 (Clinical Investigator Financial Disclosure Form).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The final CMC review is pending at this time. Dr. Parmoda Maturu's preliminary findings are that there are no approvability issues at this time.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The final pharmacology/toxicology review is pending at this time. However, Dr. Carlic Huynh's preliminary assessment is as follows: There were no nonclinical studies submitted in this NDA. The formulation is identical to the approved 0.4 mg dosage strength formulation with the exception of 2 mg of naloxone hydrochloride in this submission. The 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 was done appropriately with harsh solvents, and the leachable profile is not expected to be worse with only (b) (4) present at levels that do not represent a nonclinical safety concern. From a pharmacology toxicology perspective, the 2 mg dosage strength of EVZIO naloxone hydrochloride auto-injector is recommended for approval.

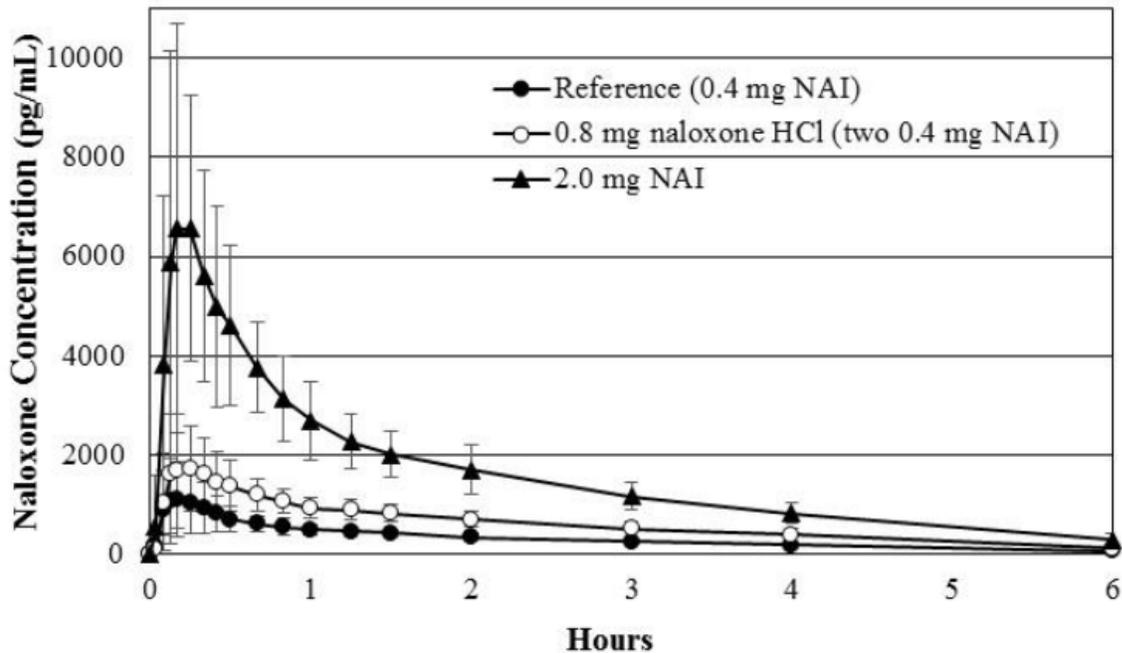
4.4 Clinical Pharmacology

Study KA-900DV-05A, a randomized, single-dose, three-sequence, three-period crossover dose proportionality study in 24 healthy subjects, was the key study supporting the dose proportionality of 0.4 mg NAI to 2.0 mg NAI. The treatments included a single 0.4 mg NAI, a 0.8 mg naloxone HCl using two 0.4 mg NAI given 2 minutes apart, and a single 2.0 mg NAI. In this study, the Applicant found that naloxone exposure (AUC) was dose proportional for the primary comparison of 2.0 mg naloxone HCl and 0.4 mg naloxone HCl administered using NAIs. In addition, linear regression indicated that naloxone exposure was linear within the dose range of 0.4 to 2.0 mg naloxone HCl following IM (intramuscular) or SC (subcutaneous) administration using NAIs.

Dr. Wei Qiu's final Clinical Pharmacology review is pending at this time. However, key findings, as taken verbatim from her preliminary review, are as follows:

In this current submission, sponsor included a PK and dose proportionality study KA-900DV-05V comparing the proposed 2.0 mg NAI and the approved 0.4 mg NAI. Study KA-900DV-05A is a randomized, single-dose, three-sequence, three-period crossover dose proportionality study in 24 healthy subjects. All 24 subjects completed the study. The treatments include a single 0.4 mg NAI, a 0.8 mg naloxone HCl using two 0.4 mg NAI given 2 minutes apart, and a single 2.0 mg NAI. Study drug was administered on Day 1, Day 2, and Day 3. All injections were given in the mid-anterolateral aspect of the thighs. Blood samples for PK determination were collected pre-dose and at 2, 5, 7.5, 10, 15, 20, 25, 30, 40, and 50 min and 1, 1.25, 1.5, 2, 3, 4, and 6 h post-dose. Naloxone plasma concentration was determined by a validated LC/MS/MS analytical method which was utilized for the comparative BA Study IJ-900DV-03O submitted in the original NDA. Lower limit of quantification is 2 pg/mL. For all QCs (5.00, 12.0, 45.0, 160, and 750 pg/mL), inter-assay precision (%CV) is 3.33 to 5.06% and inter-assay accuracy (% bias) is -2.13 to 1.22% difference from theoretical.

Figure 1. Mean Naloxone Plasma Concentration Time Profiles



Dr. Wei Qiu's Clinical Pharmacology review.

Table 2. 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

Dr. Wei Qiu's Clinical Pharmacology review.

- The PK of a single 2.0 mg NAI is adequately characterized in Study KA-900DV-05A. Mean C_{max} of 7.90 ng/mL was reached at a median T_{max} of 15 min. The mean T_{1/2} is 1.53 h. The median T_{max} and mean T_{1/2} values were similar for the 2.0 mg NAI and 0.4 mg NAI. At each time points, naloxone concentrations for the 2.0 mg NAI are greater than the 0.4 mg NAI.
- Dose proportionality for naloxone AUC_t and AUC_{inf} was demonstrated between 0.4 mg NAI and 2.0 mg NAI because the 90% CIs for the geometric mean ratios of dose normalized AUC_t or AUC_{inf} were contained within the bioequivalence criteria (0.80, 1.25). Naloxone C_{max} values were slightly greater than dose proportional for the same treatment comparison because the geometric mean ratio of the dose normalized C_{max} values was 1.24 with the upper bound of the 90% CI (1.04, 1.49) greater than 1.25.
- From clinical pharmacology perspective, sponsor has adequately characterized the PK of the proposed new strength of NAI (2 mg) and dose proportionality between 0.4 mg NAI and 2 mg NAI. According to the approved labeling for Narcan (naloxone HCl injection), the list drug product identified for NAI in the original NDA submission, an initial dose of 0.4 to 2.0 mg is given IV (or via IM/SC

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administration if IV route is not available). In the original NDA, the 0.4 mg NAI exhibited slightly (15%) greater C_{max} and equivalent AUC values of naloxone in comparison to the 0.4 mg naloxone HCl delivered via a standard syringe. Greater C_{max}, AUC, and naloxone concentrations at each time point for the 2.0 mg NAI than the 0.4 mg NAI support the addition of the new strength for the indication of opioid overdose.

Reviewer's comments: Dr. Qiu's overall assessment is that dose proportionality for naloxone AUC_t and AUC_{inf} was demonstrated between 0.4 mg NAI and 2.0 mg NAI because the 90% CIs for the geometric mean ratios of dose normalized AUC_t or AUC_{inf} were contained within the bioequivalence criteria (0.80, 1.25). This conclusion is in agreement with the Applicant.

4.4.1 Mechanism of Action

As taken from the approved Evzio 0.4 mg label:

Naloxone hydrochloride is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites.

Naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation, and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

4.4.2 Pharmacodynamics

As taken from the approved Evzio 0.4 mg label:

When naloxone hydrochloride is administered intravenously, the onset of action is generally apparent within two minutes. The time to onset of action is shorter for intravenous compared to subcutaneous or intramuscular routes of administration.

The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride.

4.4.3 Pharmacokinetics

See Section 4.4 above (Clinical Pharmacology).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The initial clinical development program for 0.4 mg naloxone auto-injector (NAI) during the original NDA approval consisted of a single comparative bioavailability study, IJ-900DV-03O, which used the to-be-marketed formulation of the product and six Human Factors studies (INT0803, INT0801, INT-FE-0901, IJ-1000FE-03O, IJ-1001FE-03O, and IJ-1025SE-03O), none of which involved the administration of the investigational medicinal product (IMP). See the Medical Officer (MO) review of the original NDA for a full discussion of these studies. Study IJ-900DV-03O is discussed in further detail in Section 7, Safety, as this study is included for pooled safety data.

New data included in this supplemental NDA submission include the following:

- **Key Bioequivalence and Dose Proportionality Study:** Study KA-900DV-05A is the key clinical bioequivalence study required to support the 2.0 mg NAI. This was a randomized, single-dose, three-period crossover bioavailability, dose proportionality, safety, and tolerability study in healthy human subjects. The PK profiles for 0.4 mg NAI, 0.8 mg naloxone HCL (two 0.4 mg NAI injections), and 2.0 mg NAI were characterized. Dose proportional naloxone exposure was demonstrated between 0.4 and 2.0 mg NAI.
- **Product Label Differentiation Study:** The product label differentiation study was conducted to evaluate if participants could successfully differentiate between the 0.4 mg NAI and the proposed 2.0 mg NAI device and cartons. The study enrolled 33 participants including 6 laypersons, 16 pharmacists, and 11 pharmacy technicians. The Applicant determined that the results of the product label differentiation study demonstrated that the carton and auto-injector label designs for the 0.4 mg NAI and the 2.0 mg NAI have acceptable differentiation for the intended use, users, and use environments. The Agency's Division of Medication Errors review of the study is currently pending.
- **Comparative Usability Studies:** Two Human Factors comparative usability studies (IJ-1026SE-03O and IJ-1027SE-03O) were conducted after the initial NDA submission and summaries of the studies were included in this submission. These studies were conducted in simulated use environments to evaluate critical task performance (identified a priori as critical for successful naloxone administration), Instruction for Use (IFU) task performance, task completion time, and user preferences. These studies, according to the Division of Medication Error Prevention and Analysis (DMEPA) reviewer, did not use the 2.0 mg NAI and so were not formally reviewed by DMEPA for this sNDA.

Features of the key studies supporting 2.0 mg NAI (Study KA-900DV-05A) and 0.4 mg (Study IJ-900DV-03O) are shown below in the table.

Table 3. Table of Clinical Studies

Study	Design	Population	Number	Relevance
Key Supportive Study for 2.0 mg NAI				
KA-900DV-05A	Randomized, single-dose, six sequence, three period crossover	Healthy	N=24	Bioavailability, safety, dose proportionality and characterization of the PK profile for 0.4 mg NAI, 0.8 mg NAI (two 0.4 mg NAIs), and 2 mg NAI
Key Supportive Study for 0.4 mg NAI				
IJ-900DV-03O	Randomized, single blind, single dose, two sequence, two period crossover	Healthy	N=30	Relative bioavailability analysis of naloxone plasma concentrations for a single IM or SC injection of 0.4 mg naloxone HCL administered using NAI or a standard syringe to provide a clinical bridge to the LD (Narcan)

Reviewer; NAI=naloxone auto injector; LD= listed drug; IM=intramuscular; SC=subcutaneous

An information request was sent to the Applicant on August 30, 2016 informing them that a 120-day safety update had not been submitted and the Applicant was advised to provide any additional safety information relevant to Evzio 2 mg received since the initial submission on April 19, 2016. The Applicant reported that all data was reported in the sNDA and no additional clinical safety data for the 2.0 mg NAI had been received.

5.2 Review Strategy

Study KA-900DV-05A is the key dose-proportionality and PK study which was used to determine that 2.0 mg naloxoxone auto-injector (NAI) is dose proportional to 0.4 mg NAI. This study is discussed in detail in Section 5.3. Key safety data from Study IJ-900DV-03O to support 0.4 mg NAI and Study KA-900DV-05A are presented in Section 7, Safety.

5.3 Discussion of Individual Studies/Clinical Trials

Only study KA-900DV-05A, discussed below, was submitted to support safety of the 2.0 mg dose.

Title: A Randomized, Three-Sequence, Three-Period, Pharmacokinetic Bioavailability and Dose Proportionality Study of Naloxone Hydrochloride Administered Using a Naloxone Auto-Injector in Healthy Human Volunteers

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Protocol Number: KA-900DV-05A

Phase: Phase 1

Date of Final Protocol: July 23, 2015; Conducted at one center in Baltimore, MD

Amendments: There were no amendments to the protocol

Primary Objectives: 1) To evaluate the dose proportionality of 0.4 mg and 2.0 mg naloxone hydrochloride (HCl) following the intramuscular (IM)/subcutaneous (SC) injection using a naloxone auto-injector (NAI); 2) To characterize the pharmacokinetic (PK) profiles of 0.4 mg, 0.8 mg (two 0.4 mg injections), and 2.0 mg naloxone HCl following IM/SC injection using NAIs.

Secondary Objective: To assess the safety and tolerability of 0.4 mg, 0.8 mg, and 2.0 mg naloxone HCL injection using NAIs.

Population: Healthy male and female subjects between the ages of 18 and 55 years, inclusive.

Duration: The duration for each subject was to have been less than 5 weeks (up to 4 weeks for screening and 4 days for in-patient admission) to complete three dosing periods

Study drugs (Investigational Medicinal Products):

- Reference: Naloxone HCL for injection at a concentration of 1.0 mg/mL (i.e., 0.4 mg/0.4 mL administered using a NAI (Evzio)
- Test: Naloxone HCL for injection at a concentration of 5.0 mg/mL (i.e., 2.0 mg/0.4 mL administered using a NAI)

Study Overview: Twenty-four (24) healthy, adult subjects were to have been enrolled and receive investigational medicinal product (IMP) in the study. Subjects were to have received the following 3 treatments in randomized order on consecutive days during in-patient treatment: a single injection of 2.0 mg naloxone HCl for injection USP administered using NAI, a single injection of 0.4 mg naloxone HCl for injection USP administered using NAI, and a 0.8 mg naloxone HCl dose (administered using two 0.4 mg NAIs given 2 minutes apart). All injections were to be given in the mid-antrolateral aspect of the thighs. Blood was to have been collected 5 minutes prior to dosing and 2, 5, 7.5, 10, 15, 20, 25, 30, 40 and 50 minutes and 1, 1.25, 1.5, 2, 3, 4, and 6 hours post-dose for each of the 3 dosing periods.

Key Inclusion Criteria:

1. Male or female subjects between the age of 18 and 55 years (inclusive) at Day -1 (admission).
2. At Day -1 (admission), Body Mass Index (BMI) between 18.5 and 32 kg/m², inclusive and a weight of ≥ 50 kg and ≤ 100 kg.
3. Female subjects must be:
 - a. Either postmenopausal, defined as at least two years without any menses before the Screening, or documented surgically sterile at least one month before Screening (in questionable cases, a blood sample with simultaneous follicle stimulating hormone and estradiol levels consistent with menopause was to be collected OR
 - b. If of childbearing potential (defined as not surgically sterile at least one month before Screening and premenopausal or less than two years postmenopausal), must have had a negative pregnancy test at the Screening Visit and Day -1 (admission) and must have been using highly effective contraception (defined as established, consistent use of oral, injected, or implanted hormonal methods of contraception established for at least 90 days before Day -1 (admission) and commit to continuing its use for 28 days after final study drug administration; placement of an intrauterine device or intrauterine system, barrier methods of contraception such as condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository), double barrier method or abstinence.
4. Male subjects and their female spouses/partners who are of childbearing potential must have been using highly effective contraception consisting of two forms of birth control (one of which must have been a barrier method) starting at the Screening Visit and commit to continuing its use for 28 days after final study drug administration.
5. No clinically significant abnormal findings on the physical examination, medical history, ECG, or clinical laboratory results during Screening or Day-1 (admission)
6. Blood pressure (BP), pulse and other vital signs within clinically acceptable ranges at the Screening Visit and Day-1 (admission).

Key Exclusion Criteria

1. A history of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results.
2. A history of diabetes or cardiac risk factors that would place the subject at increased risk for cardiovascular events or prior use of potentially cardiotoxic drugs.
3. A history of allergic or adverse responses to naloxone HCL.
4. A history of unusual bruising or prolonged bleeding.
5. Consumption of xanthines (caffeine, theobromine) in coffee, cola, or tea during the 24 hours preceding Day –1 (admission) or during the study.
6. Blood donation within 56 days of Day –1 (admission) or plasma donation within 14 days before Day –1 (admission).
7. Participation in a clinical study within 30 days before Day –1 (admission).
8. Use of any over-the-counter (OTC) medication, including topical medications such as eye drops or nose drops, vitamins, alternative and complementary medicines (including herbal formulations) or food or drink containing grapefruit juice within 14 days before Day –1 (admission) or at any time during the study with the exception of acetaminophen (≤ 1000 mg/day) and use of OTC contraceptive products.
9. Use of any prescription medication within 14 days before Day –1 (admission) or at any time during the study, with the exception of hormonal contraceptives for women of childbearing potential.
10. Treatment with any known enzyme altering drug (e.g., barbiturates, phenothiazines, cimetidine, carbamazepine) within 30 days before Day –1 (admission) or at any time during the study.
11. Smoking or use of tobacco products within 6 months before Day –1 (admission) or at any time during the study as determined by a urine cotinine concentration >200 ng/mL.
12. Females who are trying to conceive, are pregnant, or are lactating or breast feeding at Screening and continuing through the study.
13. Female subjects who donate ova starting at Screening and continuing through the study.
14. Male subjects who donate sperm starting at Screening and continuing through the study.
15. Positive serum pregnancy test at Screening or on Day –1 (admission).
16. Positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody at Screening.
17. Positive urine screen for drugs of abuse (e.g., opioids) or blood alcohol test at Screening or Day –1 (admission).

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18. Use of alcohol within 72 hours of Day –1 (admission).
19. History of abuse of alcohol, cocaine or any other substance (e.g., any opioid) within 6 months prior to Day –1 (admission).

Key Procedures:

- Screening Period (Day -28 through Day -2)
 - After informed consent and determination of eligibility, subjects were to undergo assessments to include medical history; physical examination, 12-lead ECG and other assessments per the Schedule of Events table below.
- In-house Stay (Day -1 through Day 3)
 - Subjects were to have been admitted to the clinic on Day-1 and undergo routine laboratory assessments, vital signs, 12-lead ECG, physical examination, and other assessments per the Schedule of Events table below.
 - Day 1/Randomization: Subjects were to have been randomized to receive the following study treatments in one of six sequences (ABC, ACB, BCA, BAC, CAB, or CBA).
 - Study drug was to have been administered on Day 1, Day 2, and Day 3:
 - Treatment A: IM/SC administration of 0.4 mg naloxone HCl with a single injection using a NAI (Evzio).
 - Treatment B: IM/SC administration of 0.8 mg naloxone HCl using two 0.4 mg NAIs (Evzio) given two minutes apart. The first injection will define time 0 for the purpose of Treatment B PK sampling.
 - Treatment C: IM/SC administration of 2.0 mg naloxone HCl with a single injection using a NAI.
 - Day 2 (approximately 24 hours after receipt of the first treatment) subjects were to receive the 2nd treatment
 - Day 3 (approximately 24 hours after the 2nd treatment) subjects were to receive the 3rd treatment.

Table 4. Schedule of Activities

Evaluation	Screening Phase	In-House Phase			
	Screening (Day -28 to Day -2)	Admission (Day -1) ^a	Dosing Period 1 (Day 1)	Dosing Period 2 (Day 2)	Dosing Period 3 (Day 3)
Informed consent	X				
Eligibility criteria	X	X			
Demographics	X				
Medical history, including prior medications	X				
HIV, HBsAg, HCV	X				
Serum pregnancy test ^b	X	X			X ⁱ
Urine cotinine and drug screen	X	X			
Blood alcohol test	X	X			
Physical examination (height, weight, BMI) ^c	X	X			X ⁱ
Clinical laboratory tests (chemistry, hematology, urinalysis)	X	X			X ⁱ
12-lead ECG	X	X			X ⁱ
Vital signs	X	X	X ^d	X ^d	X ^d
Study treatment ^e			X	X	X
Injection site evaluation ^f			X	X	X
Blood samples for PK ^g			X	X	X
Monitor/record AEs and concomitant medications	X	X ^h	X	X	X
Discharge					X

Abbreviations: AEs = adverse events; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PK = pharmacokinetics

^a Subjects were admitted to the clinic on Day -1.

^b Serum pregnancy for female subjects.

^c Height at the Screening Visit only; BMI at Screening and Day -1 only.

^d Vital signs (BP, pulse, respiratory rate and body temperature) were collected between 120 and 60 minutes predose and approximately 6 hours postdose (after collection of 6 hour PK sample) and were taken in the supine position after resting for ≥ 5 minutes.

^e Treatment A, B or C was administered on the morning of Day 1, according to randomization. The alternate treatments were administered on the morning of Day 2 and Day 3.

^f Injection site evaluation predose (between 15 minutes predose and immediately before dosing) and between 60 and 120 minutes postdose and at end-of-study (after collection of the final PK blood sample).

^g Blood samples were collected 5 minutes predose (5 minutes before time 0) and at 2, 5, 7.5, 10, 15, 20, 25, 30, 40 and 50 minutes and 1, 1.25, 1.5, 2, 3, 4 and 6 hours postdose for each treatment period (In Treatment B, the time of the first injection defined time 0 for the purpose of PK sampling).

^h Included the review of medications taken since the Screening Visit as well as any change of health status since the Screening Visit.

ⁱ After collection of final blood sample for PK analysis.

Applicant's table, Protocol, p. 49

Safety Assessments:

- Vital signs: Vital signs were to have been performed between 120 and 60 minutes before dosing and 6 hours post-dose on each dosing day, taken in the supine position after resting for ≥ 5 minutes.
- Injection site evaluations: Injection sites were to have been evaluated for bleeding, bruising, erythema, swelling, induration, and pain between 15 minutes pre-dose and immediately prior to dosing and between 60 and 120 minutes post-dose on each dosing day and at the EOS (end of study) after collection of the final PK blood sample.
- Adverse events and concomitant medications were to have been collected throughout the in-house period.
- Physical examination was to have been conducted at Screening, Day-1 (admission) and on Day 3 after receiving the 3rd dose of study drug and providing the last PK sample or at early termination.

PK Sampling: Samples were to have been collected over the in-house period from 5 minutes pre-dose to 6 hours post-dose (i.e., 2, 5, 7.5, 10, 15, 20, 25, 30, 40, and 50 minutes post-dose and 1, 1.25, 1.5, 2, 3, 4, and 6 hours post-dose for each treatment period) for a total of 18 timepoints. The following key PK parameters were to have been estimated from plasma naloxone concentrations: Maximum plasma concentration (C_{max}); Time to C_{max} (T_{max}), Area under the concentration-time curve from baseline to the last measurable concentration (AUC_{0-t}), and Terminal elimination half-life (T_{1/2} life).

Criteria for Stopping the Study

- If the Investigator, the Sponsor or the Medical Monitor became aware of a condition(s) or event(s) that suggested a possible hazard to subjects if the clinical study continued, then the clinical study may have been terminated after appropriate consultation among the involved parties. The clinical study may have been terminated at the Sponsor's discretion in the absence of such a finding.
- Conditions that may have warranted termination of the clinical study included, but were not limited to:
 - The discovery of an unexpected, relevant or unacceptable risk to the subjects enrolled in the clinical study;
 - Failure to enroll subjects at the required rate;
 - A decision of the Sponsor to suspend or discontinue development of the study drug.

Statistical Analysis: All demographic, safety, and pharmacokinetic (PK) data were to have been listed and summarized in tabular format by descriptive statistics as appropriate.

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6 Review of Efficacy

Efficacy Summary

No new efficacy data were included in this submission. The Applicant plans to rely on the findings of efficacy for the reference product, Narcan. Therefore, the following Sections are not applicable:

6.1 Indication

6.1.1 Methods

6.1.2 Demographics

6.1.3 Subject Disposition

6.1.4 Analysis of Primary Endpoint(s)

6.1.5 Analysis of Secondary Endpoints(s)

6.1.6 Other Endpoints

6.1.7 Subpopulations

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

6.1.10 Additional Efficacy Issues/Analyses

7 Review of Safety

Safety Summary

The Applicant's original submission was a 505(b)(2) application referencing the approved drug, Narcan (NDA 016636), to support the clinical efficacy and safety of Evzio in the treatment of opioid related overdose. The Division agreed with the Applicant's plan to submit data from a PK study in lieu of efficacy and safety studies if the PK parameters (i.e., AUC and Cmax) were found to be bioequivalent or show greater values. The PK data was found to be bioequivalent or greater. The 0.4 mg NAI was approved on April 3, 2014. The key supportive study for safety data was Study

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IJ-900DV-03O. Overall, the safety data from study IJ-900DV-030 did not show any new safety signals for naloxone. There were no deaths, serious adverse events (SAE) or withdrawals in that study, as per the MO review for the original NDA submission.

For this supplemental NDA for Evzio 2 mg, safety is supported by Study KA-900DV-05A, a bioequivalence and PK study conducted in 24 healthy subjects. 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 (0.8 mg NAI) involved two injections.

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

Overall, there were no new safety findings identified in this submission which would alter the known risk-benefit profile of naloxone.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

I) Support of Evzio 2.0 mg: The key supportive safety study for Evzio 2.0 mg is Study KA-900DV-05A, described in detail in Section 5.3.

II) Support of Evzio 0.4 mg NAI: The key supportive safety study for Evzio 0.4 mg NAI was Study IJ-900DV-03O, a randomized, single-dose, single-blind, two-sequence, two-period crossover bioavailability, safety, and tolerability study in 30 healthy subjects has been reviewed in the MO review for the original approval and described in Section 5.1 of this review.

In this section of the review, safety findings pertain to Study KA-900DV-05A unless otherwise designated. In the pooled safety section of this review, individual findings

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from Study KA-900DV-05A are discussed first, followed by a discussion of pooled findings.

7.1.2 Categorization of Adverse Events

Adverse events for Study KA-900DV-05A were coded to a preferred term (PT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. All subjects were coded using the same MedDRA dictionary. The Applicant's categorization of adverse events is acceptable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Study KA-900DV-05A

Demographics: Overall, across all treatment groups, the mean age was 36 years, approximately 80% were Black or African American, and approximately 80% were male. No subjects had a clinically significant medical history that would exclude them from participating in the study or were taking exclusionary medications prior to dosing.

Disposition:

A total of 24 subjects were enrolled in the study and received study drug. All 24 subjects completed the study; four subjects completed each treatment sequence. The treatment sequences and subject disposition are show in the table below.

Table 5. Disposition of Subjects Study KA-900DV-05A

	Treatment Sequence (n [%])						Overall N = 24
	ABC N = 4	BCA N = 4	CAB N = 4	ACB N = 4	BAC N = 4	CBA N = 4	
Enrolled	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	24 (100.0)
Completed the Study	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	24 (100.0)
Discontinued from the Study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Treatment A = 0.4 mg naloxone (single 0.4 mg injection); Treatment B = 0.8 mg naloxone (two 0.4 mg injections); Treatment C = 2.0 mg naloxone (single 2.0 mg injection)

Applicant's table, CSR, p. 46.

There were no major protocol deviations (defined by the Applicant as those deviations that would have an impact on the subject's rights, safety, or well-being, and/or on the validity of the data for analysis). This was not a placebo-controlled study so there are no comparisons between placebo-controlled and study drug-treated subjects since all subjects received the study drug. The Applicant reported that there were some minor protocol deviations mainly resulting from procedures performed outside of the clinical study protocol specified time point/tolerance window allowance and were mostly due to difficult venous access, staff errors, and changes in the period 1 dosing time due to difficult venous access for the predose PK sample. One subject was 0.2 kg over the 100 kg upper limit inclusion criterion.

Pooled Demographics

A total of 54 subjects have received naloxone HCL delivered via naloxone auto injectors (NAIs) in two Phase 1 clinical studies. In Study IJ-900DV-03O, 30 subjects received a single dose of 0.4 mg and in Study KA-900DV-05A, 24 subjects received a single dose of 2.0 mg naloxone, a dose of 0.8 mg naloxone (two 0.4 mg), and a single dose of 0.4 mg all delivered via NAI.

The key demographics by individual study are summarized below in the table. In study IJ-900DV-03O, the majority of subjects were black/African American (67%) and female (60%) while in Study KA-900DV-05A, the majority of subjects were black/African American (80%) and male (80%).

Table 6. Demographic Parameters from Individual Clinical Studies

Variable	Study LJ-900DV-03O				Study KA-900DV-05A			
	n	Mean or Percentage*	Min	Max	n	Mean or Percentage*	Min	Max
Age (years)	30	30.8	20	43	24	35.8	24	54
Height (cm)	30	170.6	159	193	24	175.9	159	192
Weight (kg)	30	72.76	51.1	96.2	24	77.75	57.2	100.2
BMI (kg/m ²)	30	24.91	20.0	29.8	24	25.10	18.8	30.5
Gender:								
Female	18	60.0%			5	20.8%		
Male	12	40.0%			19	79.2%		
Race:								
White	9	30.0%			4	16.7%		
Asian	0	0.0%			1	4.2%		
Native Hawaiian or other Pacific Islander	1	3.3%			0	0.0%		
Black/African American	20	66.7%			19	79.2%		

n = number of subjects; BMI = Body mass index; max = maximum; min = minimum

*Continuous variables are summarized by mean; categorical variables are summarized by percentage

Data source: LJ-900DV-03O and KA-900DV-05A Clinical Study Reports Tables 14.1.2 and 14.1.3

Applicant's table, Clinical Summary, p. 31.

As shown in the table below, for the pooled analysis, the mean age was 33 years and the most were black/African American (72%) and male (57%).

Table 7. Demographic Parameters from Pooled Studies

Variable	n	Mean or Percentage*	Minimum	Maximum
Age (years)	54	33.0	20	54
Height (cm)	54	173.0	159	193
Weight (kg)	54	75.0	51.1	100.2
BMI (kg/m ²)	54	25.0	18.8	30.5
Gender: Female	23	42.6%		
Gender: Male	31	57.4%		
Race: White	13	24.1%		
Race: Asian	1	1.9%		
Race: Native Hawaiian or other Pacific Islander	1	1.9%		
Race: Black/African American	39	72.2%		
Ethnicity: Hispanic/Latino	11	20.4%		
Ethnicity: Non-Hispanic/Latino	43	79.6%		

BMI = Body mass index; N = number of subjects exposed to treatment; n = number of subjects with variable

*Continuous variables are summarized by mean; categorical variables are summarized by percentage

Data source: IJ-900DV-03O and KA-900DV-05A Clinical Study Reports Tables 14.1.2 and 14.1.3

Applicant's table, ISS, p. 8.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety population consisted of all randomized subjects who received at least one dose of study drug. All subjects received all three doses of study drug. Twenty-four subjects (100%) were included in the safety analyses.

7.2.2 Explorations for Dose Response

There were no specific studies conducted to explore a dose response.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable. No special animal and/or in vitro testing was conducted.

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7.2.4 Routine Clinical Testing

Routine clinical testing for Study KA-900DV-05A was acceptable and included vital signs, laboratory assessments, physical examination, and ECG.

7.2.5 Metabolic, Clearance, and Interaction Workup

See discussion under Section 4.4 and the Clinical Pharmacology review of Dr. Wei Qui.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See discussion under Section 2.4.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in Study KA-900DV-05A.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events in Study KA-900DV-05A.

7.3.3 Dropouts and/or Discontinuations

There were no nonfatal serious adverse events in Study KA-900DV-05A.

7.3.4 Significant Adverse Events

No significant adverse events were reported.

7.3.5 Submission Specific Primary Safety Concerns

Injection site evaluation was a predefined safety outcome. Injection site evaluations were performed predose and between one and two hours postdose for each treatment period and at the end of the study for the presence of bleeding, bruising, erythema, swelling, induration, and pain.

For the single treatments (0.4 mg Treatment A and 2.0 mg Treatment C), injections were administered to the right thigh with the first single injection in the subject's sequence being administered to the anterolateral thigh and the other single injection being administered inferior to the first injection. For the 0.8 mg (two 0.4 mg, Treatment B), injections were always administered in the left thigh (first injection into the

anterolateral thigh and second injection inferior to the first injection). Findings were reported as TEAEs.

In response to an Information Request for clarification regarding how injection site AEs were categorized, the Applicant provided the following clarification:

The Applicant evaluated injection site adverse events in two ways: 1) per protocol based on when the TEAE first appeared and 2) visual inspection based on the injection site location, each discussed below:

1. First Appearance of Injection Site AE: Adverse events (AEs) were assigned, per the Statistical Analysis Plan, as follows: “For tabulations of AEs by treatment, any AE that starts on or after administration of the period 1 dose and before the period 2 dose will be assigned to the period 1 dose. Any AE occurring after the period 2 dose and before the period 3 dose will be assigned to the period 2 dose, and any AE occurring after the period 3 dose will be assigned to the period 3 dose”. Using this criterion, erythema was experienced by 2 subjects in Treatment A (0.4 mg single injection); 5 subjects in Treatment B (two 0.4 mg injections); and 1 subject in Treatment C (2 mg injection) shown below.

Table 8. Injection Site Erythema by First Appearance

Preferred Term	Treatment A N=24 n (%)	Treatment B N=24 n (%)	Treatment C N=24 n (%)
Erythema	2 (8)	5 (21)	1 (4)

Reviewer; Treatment A=0.4 mg naloxone (single 0.4 mg injection); Treatment B=0.8 mg naloxone (two 0.4 mg injections); Treatment C=2.0 mg naloxone (single 2.0 mg injection). Adverse events of erythema were assigned to a treatment group based on the start date and time of the erythema and not based on the injection site location identified in the AE description.

2. Injection Site Location: Since each treatment had a defined injection site location, the Applicant stated that it was possible to subsequently review the erythema adverse events based on location alone (not related to when the AE first appeared). Using this criterion, there were three subjects for whom the TEAEs of erythema were noted after dosing in the subsequent dosing period and therefore are reported under the subsequent treatment. Therefore, using this criterion, erythema was experienced by 3 subjects after 0.4 mg; 4 subjects after 0.8 mg, and 3 subjects after 2.0 mg as shown in the table below.

Table 9. Injection Site Erythema by Location

Preferred Term	Treatment A N=24 n (%)	Treatment B N=24 n (%)	Treatment C N=24 n (%)
Erythema	3 (12)	4 (17)	3 (12)

Reviewer; Treatment A=0.4 mg naloxone (single 0.4 mg injection); Treatment B=0.8 mg naloxone (two 0.4 mg injections); Treatment C=2.0 mg naloxone (single 2.0 mg injection). Adverse events of erythema were assigned to a treatment group based on the injection site location identified in the AE description.

The Applicant reported that the majority of the localized erythema TEAEs were described as adjacent to the injection site and consistent with the placement of the device holes. The erythema, according to the Applicant, also appeared to be associated with the amount of force used by the personnel administering the drug (although the Applicant did not provide an explanation for how they determined this). One subject experienced injection site bruising at both injection sites for 0.8 mg NAI. There were no reports of injection site bleeding, induration, or pain.

Reviewer's comment: It does not seem to make a considerable difference in the total number of subjects who experienced erythema whether the protocol-defined criterion of onset or whether injection site location and visual inspection criteria were used. Using either criterion, erythema was noted more frequently in subjects who received two injections (0.8 mg) than those who received one injection (0.4 mg or 2.0 mg). As it specifically relates to the 2.0 mg NAI, when using visual inspection, there was a slightly higher incidence (12%) compared to when using the criteria of onset (4%). Most likely, visual inspection is more accurate and, therefore, should be the criteria used for purposes of labeling of AEs.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study KA-900DV-05A

Ten subjects experienced 15 TEAEs (treatment emergent adverse events). All were mild intensity as assessed by the Investigator except for one TEAE of headache, which was considered to be of moderate intensity.

The most frequently reported TEAE was erythema (Skin and Subcutaneous Disorders SOC) observed in all treatment groups and noted as localized erythema thought due to pressure markings from the device (ten events reported in seven subjects). All events of erythema were considered by the Investigator to be related to the study treatment.

Other TEAEs included catheter site swelling, injection site bruising, dizziness, headache, and contact dermatitis reported in one subject each. The TEAEs of headache and injection site bruising were considered by the Investigator to be possibly related or related to study drug. The TEAEs of catheter site swelling, contact dermatitis, and dizziness were considered unlikely related or unrelated. With the exception of erythema, no TEAEs occurred in more than one subject and no specific trends were noted between the three treatment groups. The Applicant states that Treatment B involved two injections which may explain why five subjects experienced erythema compared to two subjects in Treatment A and one subject in Treatment C. This explanation appears reasonable.

The number of subjects with TEAEs for Study KA-900DV-05A is shown in the table below.

Table 10. Number (Percentage) of Subjects with Treatment-Emergent Adverse Events by System Organ Class (SOC), Preferred Term, and Treatment

System Organ Class Preferred Term	Treatment A N = 24 n (%)	Treatment B N = 24 n (%)	Treatment C N = 24 n (%)
General Disorders and Administrative Site Conditions	1 (4.2)	1 (4.2)	0
Catheter site swelling	1 (4.2)	0	0
Injection site bruising	0	1 (4.2)	0
Nervous System Disorders	1 (4.2)	1 (4.2)	0
Dizziness	0	1 (4.2)	0
Headache	1 (4.2)	0	0
Skin and Subcutaneous Tissue Disorders	2 (8.3)	5 (20.8)	2 (8.3)
Dermatitis contact	0	0	1 (4.2)
Erythema [†]	2 (8.3)	5 (20.8)	1 (4.2)

N = number of subjects exposed to treatment; n = number of subjects with treatment emergent adverse events; (%) = n/N x 100; TEAE = treatment-emergent adverse event

[†] Adverse events of erythema were assigned to a treatment group based on the start date and time of the erythema and not based on the injection site location identified in the adverse event description.

Treatment A = 0.4 mg naloxone (single 0.4 mg injection); Treatment B = 0.8 mg naloxone (two 0.4 mg injections); Treatment C = 2.0 mg naloxone (single 2.0 mg injection)

Applicant's table 12-2, CSR p. 65.

Pooled Safety: Pooled safety data comes from Study IJ-900DV-03O supporting 0.4 mg NAI and Study KA-900DV-05A, supporting 2.0 mg NAI. Of the 54 subjects who received naloxone in the two studies, a total of 22 TEAEs were reported for 15 subjects (two subjects experienced TEAEs during both the 0.4 mg and 0.8 mg naloxone HCL treatment periods in Study KA-900DV-05A and were counted in both treatment groups in the table below). All of the TEAEs were considered by the investigator to be mild intensity with the exception of one moderate TEAE of headache in the 0.4 mg NAI group. Seven of the 22 TEAEs were considered by the investigator to be unrelated or unlikely related to the naloxone NAI. The possibly related, probably related, or related TEAEs were 10 events of erythema and one event each of dizziness, headache, hyperhidrosis, injection site bruising, and nausea.

The only adverse events reported by more than two subjects were erythema and dizziness. Erythema was reported by 5 (21%) subjects, 2 (4%) subjects, and 1 (4%) subjects in the 0.8 mg naloxone treatment, 0.4 mg NAI, and 2.0 mg NAI groups, respectively using first appearance of erythema (one subject experienced erythema during both the 0.4 mg and the 0.8 mg naloxone HCl treatment periods and is counted in both treatment groups). The number of subjects experiencing erythema was highest for the 0.8 mg naloxone HCl treatment; where two 0.4 mg NAI injections were given. All events of erythema occurred in the KA-900DV-05A study. This most likely is because injection site evaluation was required and a prespecified assessment in Study KA-900DV-05A whereas it was not required in Study IJ-900DV-03O. Further, erythema occurred across all treatment groups and was not restricted just to the 2.0 mg NAI.

The TEAE of dizziness was reported in two (4%) subjects in the 0.4 mg NAI group and one (4%) subject in the 0.8 mg naloxone treatment group. No subjects in the 2.0 mg NAI group experienced dizziness.

Table 11, below, presents pooled TEAEs reported in Study IJ-900DV-03O and Study KA-900DV-05A by NAI administered treatment (note that TEAEs for the listed drug used in Study 03O are not included in the table but were provided in the CSR) with erythema counted by time to onset. Table 12 displays pooled TEAEs with erythema counted using the Injection Site Location criterion.

Table 11. Pooled Treatment Emergent Adverse Events

System Organ Class Preferred Term	Treatment, n (%)		
	0.4 mg Naloxone (NAD) N = 54	0.8 mg Naloxone (two 0.4 mg NAIs) N = 24	2.0 mg Naloxone (NAD) N = 24
Total Number of Subjects Experiencing ≥ 1 AE	8 (14.8)	7 (29.2)	2 (8.3)
Gastrointestinal Disorders	1 (1.9)	0	0
Nausea	1 (1.9)	0	0
General Disorders and Administration Site Conditions	2 (3.7)	1 (4.2)	0
Catheter Site Swelling	1 (1.9)	0	0
Injection Site Bruising	0	1 (4.2)	0
Vessel Puncture Site Haematoma	1 (1.9)	0	0
Nervous System Disorders	4 (7.4)	1 (4.2)	0
Anosmia	1 (1.9)	0	0
Dizziness	2 (3.7)	1 (4.2)	0
Dysgeusia	1 (1.9)	0	0
Headache	1 (1.9)	0	0
Skin and Subcutaneous Tissue Disorders	3 (5.6)	5 (20.8)	2 (8.3)
Dermatitis Contact	0	0	1 (4.2)
Erythema	2 (3.7)	5 (20.8)	1 (4.2)
Hyperhidrosis	1 (1.9)	0	0

AE = adverse event; N = number of subjects exposed to treatment; n = number of subjects with observation

A subject is only counted once per treatment group in the 'Total Number of Subjects Experiencing ≥ 1 AE' row. A subject with more than 1 preferred term event in a System Organ Class is only counted once for that System Organ Class.

Data source: [IJ-900DV-030](#) and [KA-900DV-05A](#) CSRs Tables 14.3.1.2

Applicant's table, ISS, p. 9.

Table 12. Pooled Treatment Emergent Adverse Events (Erythema Counted by Injection Site Location)

System Organ Class Preferred Term	Treatment, n (%)		
	0.4 mg Naloxone (NAI) N = 54	0.8 mg Naloxone (two 0.4 mg NAIs) N = 24	2.0 mg Naloxone (NAI) N = 24
Total Number of Subjects Experiencing ≥ 1 AE	9 (16.7)	6 (25.0)	4 (16.7)
Gastrointestinal Disorders	1 (1.9)	0	0
Nausea	1 (1.9)	0	0
General Disorders and Administration Site Conditions	2 (3.7)	1 (4.2)	0
Catheter Site Swelling	1 (1.9)	0	0
Injection Site Bruising	0	1 (4.2)	0
Vessel Puncture Site Haematoma	1 (1.9)	0	0
Nervous System Disorders	4 (7.4)	1 (4.2)	0
Anosmia	1 (1.9)	0	0
Dizziness	2 (3.7)	1 (4.2)	0
Dysgeusia	1 (1.9)	0	0
Headache	1 (1.9)	0	0
Skin and Subcutaneous Tissue Disorders	4 (7.4)	4 (16.7)	4 (16.7)
Dermatitis Contact	0	0	1 (4.2)
Erythema*	3 (5.6)	4 (16.7)	3 (12.5)
Hyperhidrosis	1 (1.9)	0	0

AE = adverse event; N = number of subjects exposed to treatment; n = number of subjects with observation

A subject is only counted once per treatment group in the 'Total Number of Subjects Experiencing ≥ 1 AE' row. A subject with more than 1 preferred term event in a System Organ Class is only counted once for that System Organ Class per treatment.

*Subjects with erythema are counted in the treatment group based on injection site location where the erythema was noted.

Data source: IJ-900DV-03O and KA-900DV-05A CSRs Tables 14.3.1.2; KA-900DV-05A CSR Table 12-3

Applicant's table, response to Information Request.

Reviewer's comments: Overall, there are no new safety findings for Evzio 2.0 mg NAI which differ significantly from Evzio 0.4 mg NAI or which alter the known risk-benefit profile of naloxone. The events of erythema seen in the study KA-900DV-05A and not reported in study IJ-900DV-03O are likely due to the fact that injection site evaluation was required in Study KA-900DV-05A and not in Study IJ-900DV-03O.

7.4.2 Laboratory Findings

Individual clinical laboratory observed values (clinical chemistry, hematology, and urinalysis) and positive microscopic urinalysis findings were included in the submission. All subjects had at least one abnormal hematology, chemistry and/or urinalysis result at Screening and/or Day-1 and 19 of 24 (79%) subjects had at least one abnormal laboratory value at the end of study (EOS) Day 3. However, all pretreatment and posttreatment abnormal laboratory values were considered not clinically significant by

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the Investigator. No clinically significant trends or shifts were noted. There were no TEAEs related to an abnormal laboratory value.

7.4.3 Vital Signs

Although there were some abnormal vital sign measurements reported, there were no observable trends in any specific parameter or any specific treatment group. There were two instances of an individual change from baseline predose BP of ≥ 20 mmHg but these were not considered clinically significant by the investigator and were not associated with adverse events. There were no TEAEs related to abnormal vital sign measurements reported.

7.4.4 Electrocardiograms (ECGs)

No clinically notable changes were seen in group mean and median values for ECG parameters from baseline to postdose assessment on Day 3. All changes from baseline in QT, QTcB and QTcF intervals were ≤ 30 msec except for one subject who had a QTcB change from baseline of 46 msec at Day 3. The clinical significance of this is unclear as this subject (Subject 101) had no SAEs reported. No cardiac AE terms were reported. There were 21 of 24 subjects (87%) who experienced abnormal qualitative ECG findings noted predose and/or end of study assessed by the Investigator as not clinically significant.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable. No special safety studies or clinical trials were conducted.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the pooled studies, there appeared to be a higher incidence of erythema in the 0.8 mg NAI and 2 mg NAI dose strengths compared to the 0.4 mg NAI. However, the studies contributing to the safety database were not placebo-controlled and no clinically meaningful interpretation can be drawn with regard to dose dependency.

7.5.2 Time Dependency for Adverse Events

Not applicable.

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7.5.3 Drug-Demographic Interactions

No studies examining clinical safety of NAI in different demographic populations have been completed.

7.5.4 Drug-Disease Interactions

No studies examining clinical safety of NAI for drug-disease interactions have been completed.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not assessed in Study KA-900DV-05A. The proposed label is as follows:

Section 5.3: Although a direct cause and effect relationship has not been established, after use of naloxone hydrochloride, monitor patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in an appropriate healthcare setting.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant reported that human carcinogenicity or reproductive impairment potential of NAI was not specifically assessed, but no tumor-related adverse events or inadvertent drug exposure in pregnant subjects was reported.

7.6.2 Human Reproduction and Pregnancy Data

There were no reports of pregnancy in Study KA-900DV-05A or pooled studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric clinical studies are proposed because pharmacokinetic (PK) studies in healthy, pediatric patients would involve more than minimal risk without the prospect of direct benefit to the population. Furthermore, PK studies cannot be conducted in a pediatric opioid overdose population because it is an immediately life-threatening condition and PK samples cannot be collected in the context of emergency treatment of the overdose, in addition to other ethical considerations that preclude conducting studies.

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The Sponsor submitted a Pediatric Study Plan for Evzio 2.0 mg on September 22, 2015 which was agreed to by the Agency on October 16, 2015. The pediatric plan relies upon the safety and effectiveness of other naloxone hydrochloride products in the post-marketing setting as well as data available in the medical literature, clinical practice guidelines, and approved labeling for the 0.4 mg auto-injector to support the pediatric labeling.

The Applicant is seeking approval of 2.0 mg NAI for the treatment of all pediatric populations as an initial dose in cases of opioid overdose. However, the Applicant states that because the dose of naloxone provided by the 2.0 mg NAI is higher on a weight basis for neonatal patients, they recommend new labeling to provide guidance to consider weight-based dosing in neonates to avoid abrupt precipitation of opioid withdrawal symptoms.

Applicant's proposed labeling:

(b) (4) of the Prescribing Information:

There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. (b) (4)

Section 8.4 of the Prescribing Information:

In settings (b) (4) where it may be preferable to avoid the abrupt precipitation of opioid withdrawal symptoms, consider use of an alternate naloxone- (b) (4) product that can be dosed according to weight and titrated to effect.

The Division of Pediatric and Maternal Health (DPMH) has been consulted to assist in the review of the submitted pediatric information, label, and approval recommendations including the Pregnancy and Lactation Labeling Rule (PLLR) language. The Pediatric and Maternal Health consults are pending at this time.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no clinical experience with naloxone HCL with regard to overdosage, drug abuse potential, or withdrawal and rebound in humans.

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7.7 Additional Submissions / Safety Issues

No additional safety studies or updates were submitted for review. A clinical information request was sent to the Applicant on August 29, 2016 informing them that a 120 day safety update had not been submitted. The Applicant informed the Division that they had received no new safety data relevant to NAI 2mg since the supplemental NDA was submitted. Relevant safety related to NAI 0.4 mg is discussed in Section 8, Postmarket Experience, below.

8 Postmarket Experience

In response to an Agency information request, the Applicant provided a comprehensive safety analysis of the postmarketing data for the approved Evzio 0.4 mg NAI with particular areas of interest on the following terms: drug or device ineffective, device failures, and events in the pediatric population.

The Applicant reported that since commercial launch of Evzio 0.4 mg (July, 2014) through April 3, 2016, a total of (b) (4) domestic packages (two Evzio auto-injectors and one Trainer for Evzio) were distributed through commercial sale, donation, or patient assistance programs.

During this period, a total of 11 initial cases were reported for subjects experiencing at least one adverse event after receiving Evzio 0.4 mg NAI. A follow-up report was provided for one case report. As shown in the table below, the preferred term Drug Ineffective was reported in four cases (most frequently reported AE term), followed by the preferred term Disorientation which was reported in three cases. Detailed narratives and discussion of the terms of interest are discussed following the table.

Table 13. Number of Persons with Reported Post-Marketing Adverse Events for Evzio by System Organ Class and Preferred Term

System Organ Class Preferred Term	EVZIO (naloxone HCl) 0.4 mg
Total Number of Persons Experiencing ≥ 1 Adverse Event	11
General Disorders and Administrative Site Conditions	7
Drug ineffective	4
Drug withdrawal syndrome	1
No adverse event ¹	2
Injury, Poisoning and Procedural Complications	2
Accidental exposure to product ¹	2
Psychiatric Disorders	5
Agitation	1
Anger	1
Confusional state	1
Disorientation	3

A person is only counted once in the 'Total Number of Persons Experiencing ≥ 1 Adverse Event' row. A person with more than 1 preferred term event in a System Organ Class is only counted once for that System Organ Class.
¹ For the two persons who experienced "Accidental exposure to product", reports of "No adverse event" were also noted in both cases.

Applicant's table, response to Agency Information Request.

- Deaths: Of the 11 case reports, two were 15-day post-marketing alert reports with outcome of death. It is my assessment that in both of these cases, the subjects may have already died by the time Evzio was received or, at least, the Evzio was received too late to reverse overdose. The narratives for these cases are provided below:
 - EVZI20150010: This was a spontaneous report received from a police department of a 49-year-old male who experienced cardiorespiratory arrest from a suspected heroin overdose. The patient's medical history included heroin use and a possible infection of unknown etiology for approximately two days according to his roommate. Concomitant medications were unknown. Police officers were called for an unresponsive subject who was not breathing. According to the roommate, the patient's last use of heroin was unknown. Three hours before the police arrived, the patient was having labored breathing and pain of an unknown location. When the police arrived, the patient was not breathing and there appeared to be blood or a similar dark, viscous fluid on his shirt, along his arms, and in and around his mouth. There were 13 syringes and a glass smoking pipe in his apartment. The officer continued CPR and administered one injection of Evzio to the outer thigh. There was no response and the subject was subsequently transported to

- a hospital where he was declared dead. An autopsy was reportedly scheduled but results were not provided in the narrative. This case was also listed as drug ineffective.
- EVZI20150012: This was a spontaneous report received from a television media station where it was reported that “in all but one case when police officers had used the Evzio injector, it had been successful.” The follow-up with the police department revealed that the male victim who did not respond to Evzio injection was suspected to have taken a heroin overdose and subsequently expired. It was reported that he “was down too long to be successfully resuscitated.” Nonetheless, he was administered one Evzio injection without response. A follow-up report revealed that the patient was a 44-year old man who was found to be “purple and pulseless” approximately 26 minutes after initial information was received by his girlfriend. The officers administered one dose of Evzio without response. Rescue personnel arrived and continued resuscitation efforts without success for approximately 20 minutes. Additional medical history included previous drug use. The only known concomitant medication was gabapentin. This case was also classified as drug ineffective.
 - Drug Ineffective: There were four case reports of drug ineffective and one follow-up reported with narratives as follow:
 - EVZI2015006: This was an adult male of unknown age who was administered two Evzio injections for heroin overdose and did not respond. This person reportedly “did a shot of heroin and collapsed face down on the floor.” He was not breathing (turning blue) and was non-responsive. He was given the first 0.4 mg Evzio on his thigh through his pants and there was no response. His pants were pulled down and he was given the second injection directly on this thigh. There was no response so he was given in sequence two intranasal naloxone doses of unknown strength. After the third dose of intranasal naloxone, he responded with some restored breathing. He reportedly had “complete restoration of consciousness”. No additional information was provided.
 - EVZI20150010: See death narrative above under Deaths.
 - EVZI20150012: See death narrative above under Deaths.
 - EVZI20150013: This was the case of a subject who was found by his friend “turning blue” and hard to arouse. The friend had been trained to use Evzio and administered one injection to the patient’s outer thigh. The friend stated that he did not think the needle protruded because he said the audio kept repeating “the device is ready to use” and there was no “popping sound” when applied to the thigh which he said he had previously heard when he administered Evzio. He did not observe whether the viewing window was clear or not. The patient did not respond until medical personnel arrived and administered IV naloxone. The patient then recovered completely. The Sponsor reported that the

Evzio auto-injector which had been used was discarded by the time the event was reported to the clinic. This case was also considered as possible device failure.

- Possible Device Failure: See Narrative EVZI20150013 above under Drug Ineffective.
- Accidental Pediatric Exposure:
 - EVZI20150014: This was a 17-year old male (a student) who injected himself with the Evzio injector while observing a demonstration on the treatment of opioid overdoses with Evzio. The subject reportedly took one Evzio auto-injection and injected himself in the thigh. It was unknown if the student knew if he was taking Evzio or the trainer. The student experienced no adverse events at the time. The person giving the demonstration did report the event to the school superintendent but no additional information was provided. This was considered an accidental exposure.

Reviewer's comment: Although there were two deaths reported, reviews of the narratives for these cases suggest that the subjects most likely did not receive Evzio in time to reverse the overdose effects. There is no definite evidence, based upon the review of the narratives, of a defective device.

9 Appendices

9.1 Literature Review/References

The Applicant conducted a literature review which was presented in the original NDA submission and was previously reviewed in the initial Medical Officer (MO) review. The Applicant reports that the development of the 2.0mg NAI does not impact the data presented in the original NDA.

In the original NDA submission, the Applicant submitted an analysis of a PubMed database search or published data relevant to the safety and efficacy of naloxone through June 9, 2013. In addition, at the Division's request, an additional submission was submitted on March 17, 2014 which included an analysis of the literature to support Section 6 of the approved label.

For this supplemental NDA, the Applicant reported that in addition to the review and searches conducted through June 9, 2013 to support the initial application for NAI approval, they also conducted Medline and Embase database searches for safety literature relevant to NAI and naloxone since the marketing of 0.4 mg NAI in July, 2014. They identified no serious, unlabeled adverse events regarding safety of the drug

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product based on their literature search. The Applicant reported that there was no update in this information for this supplemental NDA.

In general, I have categorized the Applicant's literature summaries as follows:

- Primarily Efficacy:
 - Pharmacodynamic/Efficacy Studies – 10 studies
 - Restrospective and Observational Studies in a Suspected Overdose Population – 7 studies
 - Naloxone HCL Distribution Program Findings in a Suspected Opioid Overdose Population – 11 studies
- Primarily Safety
 - Naloxone HCL – 3 studies
 - Case Reports – 4 Reports
 - Prospective Studies – 2 studies
 - Extremely High Doses of Naloxone – 5 studies

I agree with the Medical Officer (MO) reviewer's assessment as stated in the original NDA that the analysis of the literature does not raise any concerns about the safety and effectiveness of naloxone for the treatment of respiratory depression secondary to opioid overdose. Naloxone is the standard of care, with no absolute contraindications, for the treatment of opioid-related respiratory depression regardless of age, sex, or ethnicity. Cardiovascular events, pulmonary edema, and seizures have been reported and studied in the literature. However, separating the effects of naloxone from the effects of concomitant medications and pre-existing disorders has been problematic. High doses of naloxone have been administered in clinical trials and generally have been well tolerated. Overall, naloxone is considered to have a wide safety margin. Review of the Applicant's summarized data of the provided literature reveals no new safety signals that would alter the risk-benefit profile of Evzio in this population.

9.2 Labeling Recommendations

The label is currently under review within the Division. At present the following areas will need further internal discussion and input from the upcoming Advisory Committee and the Division of Pediatric and Maternal Health consultants:

- Clarification regarding criteria for determining dose selection of 0.4 mg NAI versus 2.0 mg NAI
- Pediatric labeling

9.3 Advisory Committee Meeting

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AC) and the Drug Safety and Risk Management Advisory Committee (AC) is to be held on October 5, 2016. That meeting will address issues related to the class of naloxone products. The agenda for that meeting has not been finalized.

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9.4 Appendix (Clinical Investigator Financial Disclosure)

Clinical Investigator Financial Disclosure

Application Number: 205787

Submission Date: April 19, 2016

Applicant: Kaleo, Inc.

Product: Naloxone Auto-injector (NAI), 2 mg

Reviewer: Elizabeth Kilgore, MD

Date of Review: September 5, 2016

Covered Clinical Study (Name and/or Number): KA-900DV-05A

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>6</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>This section is Not Applicable (N/A) as there were no investigators with disclosable financial interests/arrangements.</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:</p> <p>Significant payments of other sorts:</p> <p>Proprietary interest in the product tested held by investigator:</p> <p>Significant equity interest held by investigator in sponsor of covered study:</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/> N/A	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/> N/A	No <input type="checkbox"/> (Request information)

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		from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/> N/A	No <input type="checkbox"/> (Request explanation from applicant)

(N/A=not applicable)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.

The disclosed financial interests/arrangements do not affect the approvability of the application.

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

/s/

ELIZABETH M KILGORE
09/16/2016

JOSHUA M LLOYD
09/16/2016



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Medical Officer Filing Review Memo

NDA: 205-787
Drug Product: Naloxone Auto-Injector (NAI) (brand name Evzio)
Sponsor/Applicant: kaleo, Inc.
Type of Submission: Supplemental NDA (S-007)
Date of Submission: April 19, 2016 (electronic)
Date of Receipt: April 19, 2016 (electronic)
Supporting Document: Number 187
Reviewer: Elizabeth Kilgore, MD
Team Leader: Joshua Lloyd, MD
Project Manager: Diana Walker

Injectable naloxone HCL 0.4 mg (Tradename Evzio) was approved on April 3, 2014, under NDA 205,787 for use in pediatric and adult patients of all ages to facilitate administration of naloxone hydrochloride (HCL) by family members, caregivers, and/or bystanders (i.e., laypersons) in the non-healthcare setting for reversal of opioid overdose. Each injection of Evzio delivers 0.4 mg naloxone hydrochloride injection (0.4 mL) in a pre-filled auto-injector.

Evzio is indicated for *the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression and is intended for immediate administration as emergency therapy in settings where opioids may be present.*

On April 19, 2016, kaleo, Inc. (Sponsor/Applicant) submitted a supplemental New Drug Application (sNDA) to market a 2 mg dose of Evzio (2.0 mg/0.4 mL). The 2 mg dose is proposed to be indicated for the same indication as the currently approved 0.4 mg dose.

The Applicant submitted a pharmacokinetic study (KA-900DV-05A), literature, and proposed labeling in support of the 2 mg dose. In particular, the Applicant referenced literature to support the efficacy and safety of the 2 mg dose in the entire pediatric population, as was done for the 0.4 mg dose and included an Agreed Pediatric Study Plan. The Division of Pediatric and Maternal Health (DPMH) will be consulted to evaluate the literature submitted to support labeling in pediatrics. Although the proposed labeling contains updated pregnancy and lactation labeling consistent with the Pregnancy and Lactation Labeling Rule (PLLR), the Applicant did not submit the clinical

data from the literature to support that labeling, as is required. Additionally, the proposed labeling contains (b) (4)

The Applicant's proposed labeling includes both the 0.4 mg and 2 mg dose and states the following:

Initial Dosing: Administer the initial dose of EVZIO to adult or pediatric patients intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary, and seek emergency medical assistance. Administer EVZIO as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death.

Repeat Dosing

The requirement for repeat doses of EVZIO depends upon the amount, type, and route of administration of the opioid being antagonized. If the patient responds to EVZIO and relapses back into respiratory depression before emergency assistance arrives, (b) (4)

If the desired response is not obtained after 2 or 3 minutes, administer an additional dose of EVZIO (b) (4). If there is still no response and additional doses are available, administer additional doses of EVZIO every 2 to 3 minutes (b) (4) until emergency medical assistance arrives. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

(b) (4)

The Applicant did not provide information or data to describe how a prescriber would select the most appropriate dose in advance of an opioid overdose event or how laypersons would determine if it is clinically appropriate to use the 2 mg dose versus the 0.4 mg dose, if more than one dose is available at the time of an opioid overdose. This issue was discussed at the filing meeting and will be the subject of an upcoming Advisory Committee meeting.

The application initially did not contain an analysis of postmarketing safety data for the 0.4 mg dose, which is an important component of the evaluation, particularly from a device failure/malfunction, adverse event, and lack of efficacy perspective. The Applicant has subsequently submitted this information to the NDA in response to an information request. The application otherwise contains sufficient information, including

an integrated summary of safety (ISS), integrated summary of effectiveness (ISE), summary of clinical safety (SCS), and summary of clinical effectiveness (SCE).

The application is appropriately formatted and organized in a manner to allow a substantive review and contains the necessary information from the clinical perspective.

Recommended Regulatory Action: The sNDA is fileable from the clinical perspective with the following comments for the 74-day letter:

1. Your prescribing information (PI) must comply with the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements [see Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014), codified at 21 CFR 201.56 and 201.57(c)(9)]. Although you have submitted the PI in PLLR format, the submission must include a review and summary of the available published literature regarding drug use in pregnant and lactating women, which should be located in Module 1. Submit the integrated summary to your NDA as soon as possible. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

2. Although you did not provide a separate annotated label, you have provided annotation comments in the Word version of your package insert. Your annotated labeling contains



(b) (4)

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

/s/

ELIZABETH M KILGORE
06/08/2016

JOSHUA M LLOYD
06/08/2016