CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215457Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 28, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215457
Product Name and Strength:	Naloxone hydrochloride injection, 10 mg
Applicant/Sponsor Name:	Kaleo, Inc.
OSE RCM #:	2021-1732-1
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU) received on February 25, 2022 for naloxone hydrochloride. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised IFU for naloxone hydrochloride (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous human factors results review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Bhalodia, A. Human Factors Results Review for naloxone hydrochloride (NDA 215457). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 26. RCM No.: 2021-1732.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 25, 2022

- Instructions for Use (Image not shown) received on February 25, 2022, available from \\CDSESUB1\evsprod\nda215457\0023\m1\us\114-label\1141-draft-label\ifu-pat-info-ij5060-00.pdf

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/s/

AVANI BHALODIA
02/28/2022 11:28:13 AM

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02/28/2022 11:36:49 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	Date
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215457
Product Name and Strength:	naloxone hydrochloride injection, 10 mg (25 mg/mL) autoinjector
Applicant/Sponsor Name:	Kaleo Inc.
OSE RCM #:	2021-1731-1
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, outer case labeling, carton labeling, prescribing information (PI), and information for use (IFU) received on February 11, 2022 for naloxone hydrochloride. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label, outer case labeling, and carton labeling, PI, and IFU for naloxone hydrochloride (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Birkemeier D. Label and Labeling Review for naloxone hydrochloride (NDA 215457). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 NOV 22. RCM No.: 2021-1731.

APPENDIX A. IMAGES OF LABEL AND LABELING

Prescribing Information (Image not shown) received on February 16, 2022

NDA 215457_USPI
sent to Applicant da

Instructions for Use (Image not shown) received on February 16, 2022

NDA 215457_IFU
sent to Applicant da

Carton Labeling received on February 11, 2022

Outer Case Labeling received on February 11, 2022

(b) (4)

Container Label received on February 11, 2022

(b) (4)

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/s/

DAMON A BIRKEMEIER
02/17/2022 05:26:32 PM

VALERIE S VAUGHAN
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 2/8/2022

To: Jane Mun, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Nima Ossareh, PharmD, RAC Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for NALOXONE HYDRICHLORIDE INJECTION

NDA: 215457

In response to DAAAP consult request dated September 10, 2021, OPDP has reviewed the proposed product labeling (PI) for NALOXONE HYDRICHLORIDE INJECTION.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAAP on February 3, 2022, and are provided below.

PPI, IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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/s/

NIMA OSSAREH
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 4, 2022
To:	Jane Mun, PharmD Regulatory Project Manager **Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nima Ossareh, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name)/ Dosage Form and Route:	NALOXONE HYDRCHLORIDE injection, for intramuscular or subcutaneous use
Application Type/Number:	NDA 215457
Applicant:	kaleo, Inc.

1 INTRODUCTION

On August 31, 2021, kaleo, Inc. submitted for the Agency's review an original New Drug Application (NDA) 215457 under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for NALOXONE HYDROCHLORIDE injection. The proposed indications for NALOXONE HYDROCHLORIDE injection are:

(b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on September 10, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for NALOXONE HYDROCHLORIDE injection.

A separate Division of Medication Error, Prevention, and Analysis (DMEPA) review of the IFU was completed on November 22, 2021, and the Human Factors Study Report review was completed on January 26, 2022.

2 MATERIAL REVIEWED

- Draft NALOXONE HYDROCHLORIDE injection PPI and IFU received on August 31, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 3, 2022.
- Draft NALOXONE HYDROCHLORIDE injection Prescribing Information (PI) received on August 31, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 3, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

16 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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NIMA OSSAREH
02/04/2022 04:17:54 PM

SHARON R MILLS
02/04/2022 04:21:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From:	Ndidi Nwokorie, MD Medical Officer Division of Pediatrics and Maternal Health (DPMH) Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM) Office of New Drugs (OND)
Through:	Mona Khurana, MD, Pediatric Team Leader DPMH, ORPURM, OND John J. Alexander, MD, MPH, Deputy Director DPMH, ORPURM, OND
To:	Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP)
Subject:	Review of Pediatric Efficacy and Safety Assessment for Naloxone Autoinjector 10 mg (NDA 215457)
Applicant:	kaleo, Inc.
Application number:	NDA 215457
Drug:	Naloxone Autoinjector 10 mg
Drug Class:	Opiate Antagonist

Proposed Indication: (b) (4)

Route of administration: Intramuscular (IM) or subcutaneous (SC) Injection

Dosage Form: Single dose solution for injection in a prefilled pen

Dosage Strengths: 10 mg

Consult Request:

DAAP consulted DPMH on September 9, 2021 to review the safety and efficacy data submitted by kaleo, Inc (the Applicant) as well as any other available safety information supporting the safe use of Naloxone Autoinjector 10 mg (NAI 10) in pediatric patients 12 years and older and to assist in reviewing labeling as it pertains to pediatric use information.

Materials Reviewed:

Document entered in DocuBridge under NDA 215457

eCTD# 0001, August 8, 2021

- Clinical Overview
- Clinical summary
- Agreed Pediatric Study Plan

eCTD# 0009, December 1, 2021

- Response to Information Request

Accessed from Drugs@FDA on January 24, 2022

- Approved USPI for Kloxxado NDA 212045
- Approved USPI for Zimhi NDA 212854

Background:

Kaleo, Inc. submitted a new drug marketing application, NDA 218457, for Naloxone Autoinjector 10 mg (NAI 10) on August 28, 2021 for the following proposed indications:

(b) (4)

This application is subject to study requirements under the Pediatric Research Equity Act (PREA) (21 U.S.C 355c) because the Applicant is proposing a new indication and a new dosing regimen for naloxone; hence, the Applicant is required to provide an assessment of the safety and effectiveness of the product for the claimed indication(s) in the pediatric population unless the Agency agrees that study requirements may be waived in some or all pediatric age groups. This NDA includes an Agreed initial Pediatric Study Plan (iPSP) containing a plan to request a deferral in patients from birth to less than 12 years of age and an assessment concurrent with adults in patients 12 to less than 17 years of age.

Multiple naloxone hydrochloride (HCl) products are currently FDA approved in pediatric patients of all ages for the emergency treatment of known or suspected opioid overdose. (Appendix 1) Conducting controlled efficacy trials is challenging in both the adult and pediatric populations for both ethical and logistical reasons given the potential life-threatening nature of the condition if untreated or inadequately treated. In lieu of conducting clinical efficacy trials, the clinical development programs for previously approved products relied on meeting the pharmacokinetic (PK) standard publicly shared[1,2] by DAAP for adult approval. The PK standard established by DAAP requires clinical development programs for novel naloxone drug products to demonstrate comparable or greater bioavailability to an approved naloxone dose and route of administration in healthy adult volunteers. Novel naloxone products must match or exceed the PK profile of the approved naloxone product, especially during the early critical period of opioid overdose when prolonged apnea can lead to permanent hypoxic brain injury or death. The key PK parameters include the peak plasma concentration [C_{max}], time to C_{max} [T_{max}], and systemic exposure as measured by the area under the concentration time curve [AUC] during the first few minutes post-dosing. The PK studies supporting approval of novel naloxone drug products are conducted in healthy adults. Pediatric approval of novel naloxone drug products meeting DAAP's PK standard is generally supported by additional data from human factors validation testing if needed, published data supporting the safety of the proposed dosage, and nonclinical data if needed to support the safety of any novel or previously unqualified excipients present in the formulation.

Kaleo, Inc. is seeking approval of its 10 mg naloxone product in adults and pediatric patients 12 years and older. This dose is higher than previously approved naloxone products. Until recently,

[1] April 12, 2012 Public Workshop on Role of Naloxone on Opioid Overdose Fatality Prevention

[2] July 1-2, 2015 Exploring Naloxone Uptake and Use Public Meeting

the highest naloxone strengths approved for use for opioid overdose reversal were the 2 mg Autoinjector (Evzio, NDA 209862), and the 4 mg intranasal (Narcan, NDA 208411) naloxone products. Most recently, FDA approved a 5 mg prefilled syringe for intramuscular/subcutaneous (IM/SC) injection of naloxone (Zimhi, NDA 212854) and an 8 mg intranasal (IN) naloxone (Kloxxado, NDA 212045). Both of these products were approved in 2021 down to birth for the emergency treatment of known or suspected opioid overdose.

In this NDA, kaleo, Inc. is supporting its claim of safety and effectiveness in adult patients based on a comparative bioavailability study, a crossover PK study, and a PK/pharmacodynamic (PD) simulation and modeling analysis. The crossover PK study was conducted in 24 fasted healthy adults evaluating the PK profile after a single 2 mg dose by an approved Naloxone Autoinjector (Evzio) and a single 10 mg dose by this Naloxone Autoinjector. Plasma concentrations were analyzed up to 12 hours post dose. There was a 5-fold increase in the mean PK parameters of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ for 10 mg Naloxone Autoinjector compared to the 2 mg Naloxone Autoinjector, and a slightly greater than 5-fold increase for C_{max}.[3] Kaleo, Inc. conducted a PK/PD simulation and modeling analysis to support its claim for efficacy in the adult population. The Applicant used PK data obtained from healthy adult volunteers to inform a model which was used to simulate opioid-induced respiratory depression and predict the reversal of such respiratory depression after administration of naloxone 10 mg. The Applicant's analyses demonstrated that decreases in ventilation due to doses of morphine or buprenorphine could be partially reversed by a single 10 mg naloxone dose. Results also suggest that a 10 mg naloxone dose administered prior to fentanyl or carfentanil exposure reduced the severity of respiratory depression.[3]

In an Agreed Pediatric Study Plan (PSP), FDA acknowledged that the pediatric assessment in patients 12 to less than 17 years of age could rely on the PK/PD modeling program submitted to support the approval of this product in adult patients along with safety data compiled from the medical literature, clinical practice guidelines, and approved labeling for naloxone hydrochloride 1 mg/ml injection (NDA 016636) to support the pediatric safety of the proposed dosage for the proposed indications. The Applicant plans to rely on the PK data collected in adults to allow this product to bridge to FDA's previous findings of safety and effectiveness for the LD, which are labeled down to birth. This approach to support pediatric approval is generally consistent with that of other novel naloxone programs.

Literature Review

The Applicant included 5 publications (Appendix 2) in this NDA to support the pediatric safety of this product. However, only one publication[4] was relevant to the indication the Applicant is seeking.

This reviewer conducted a literature search of the PubMed and EMBASE databases from 2009 to present to identify any relevant recent publications to augment the safety data submitted by the Applicant. The following search terms were used to conduct the search:

[3] Clinical Overview eCTD# 0001, August 8, 2021

[4] Donna L. Seger & Justin K. Loden (2018): Naloxone reversal of clonidine toxicity: dose, dose, dose, Clinical Toxicology, DOI: 10.1080/15563650.2018.1450986

- ("High dose naloxone use" AND "pediatric patients") ("Naloxone" AND "pediatric" AND "dose")

- ("High dose naloxone" AND "ultra-potent opioids" AND "adolescents")

- ("Adverse Reaction" AND "naloxone" AND "pediatrics" OR "adolescent")

- ("Naloxone" AND "pulmonary edema" AND "adolescent")

After screening titles and abstracts, the following articles were discarded:

- Non-English publications
- Reviews
- Editorials

Three publications met this reviewer's search criteria and consisted of the following:

One retrospective medical chart review (also identified by the Applicant)

- 3 abstracts
  - 1 case report[5]
  - 1 case series[6]
  - 1 retrospective chart review[7] which duplicated the data described in the first publication).[4]

Seger & Loden[4] published a retrospective chart review of hospital toxicology records from 2010 to 2014. They reviewed 53 patients ranging in age from 6 months to 16 years presenting with clonidine exposures. The authors excluded one patient as he remained asymptomatic. Fifty-two symptomatic patients received naloxone for central nervous system (CNS) depression. Of the 52 patients receiving naloxone, 21 patients received 10 mg IV bolus, 1 patient received 2 doses of 5 mg IV bolus, 35 of 52 patients received an IV infusion of naloxone ranging in rate from 2-30 mg/h (mean 6.5 mg/h). Thirty-one patients received variable doses of naloxone IV: one patient received 18.4 mg, another received 13 mg and a 2-year-old patient with fluctuating mental status received a total of 60 mg naloxone during resuscitation requiring intubation for

[5] Lee S., Traxler J., Browning M., Chase P., Bilden E. "Pediatric clonidine overdose treated with 219 MG cumulative dose of naloxone" Clinical Toxicology 2019 57:10 (993-994)

[6] Acciani J., Kao L., "Pediatric buprenorphine/naloxone poisoning: A case series" Clinical Toxicology 2009 47:7 (744)

[7] Seger D., Loden J., Byrne D. "Naloxone reversal of clonidine toxicity in pediatric patients" Clinical Toxicology 2017 55:7 (749)

transport. The authors report no adverse events following any of the doses of naloxone administered.

Acciani & Kao[6] was a case series describing three pediatric patients ranging from 14 months to 3 years of age who received naloxone for treatment of buprenorphine/naloxone overdose. Two of the three patients received standard approved naloxone doses, but the third patient was a 2-year-old boy with persistent respiratory and CNS depression for which he was initially given 2 mg naloxone IN followed by an additional 2 mg IN and then placed on an IV infusion for 33 hours. He received a total of 50 mg of naloxone; the authors did not comment on his outcome. The authors did not explicitly state in the abstract whether or not any adverse events occurred in these three patients.

Lee S et al[5] was a case report describing a 23-month-old, 15 kg female with clonidine overdose who was initially given, by emergency medical personnel, 1 mg naloxone IN followed by 3 more doses of 1 mg IN in the prehospital setting. On arrival to the hospital, the patient received two 1 mg IV doses followed by 2 mg IV, 5 mg IV, and 10 mg IV boluses. The patient was then placed on an IV infusion of naloxone starting at 10 mg/h and titrated up to 15 mg/h over 24 hours. She received a total naloxone dose of 219 mg. The patient was discharged to home the following day with no reported sequelae.

Discussion

Kaleo, Inc. demonstrated through its PK/PD analysis that this product may reverse high potency opioids in certain situations in the adult population when given immediately. The Applicant's analyses further suggest that this product may be beneficial prophylactically when entering an environment with suspected aerosolized ultra-potent opioids. Thus, kaleo, Inc. has established an effective dose of its product, naloxone autoinjector, to reverse the effects of high-potency opioids. Given that this product is expected to produce greater exposures of naloxone and the risks of high dose naloxone are unknown, this reviewer searched the literature for evidence supporting the pediatric safety of the proposed 10 mg dose injectable. The literature supporting the safe use of 10 mg naloxone in the pediatric population is limited and a literature search yielded 3 recent publications. However, these published reports demonstrate that pediatric patients have been exposed to high doses of naloxone with no reported adverse events. There is a theoretical concern that a larger bolus of naloxone may precipitate withdrawal in opioid-dependent patients. There are some pediatric patients who may be opioid dependent, particularly older adolescents with a substance abuse disorder. Administration of naloxone in such patients could theoretically result in an acute withdrawal syndrome. However, in mass casualty situations, where there is known or suspected exposures to high-potency opioids, adolescents exposed to such threats could benefit from this higher naloxone dose where rapid higher plasma concentration of the naloxone would be beneficial in reversing the opioid overdose and thus increase the probability of survival. In such

situations the risks of an acute withdrawal syndrome, which is manageable with appropriate care, is outweighed by the potential prevention of death from the ultra-potent opioid exposure. Likewise, there may be civilian responders younger than 18 years of age who may be deployed into a mass casualty situation with known or suspected ultra-potent opioid exposure who would benefit from this novel naloxone product.

Appendix 1:

Table 1 Current Naloxone Treatment Options

Drug Product Name	NDA	Approval Date	Dose Form
Narcan (1mg/ml)	016636	4/13/1971	Solution for injection
Narcan Nasal Spray (4 mg)	208411	11/18/2015	Nasal Spray
EVZIO (Naloxone HCl) (2 mg) (discontinued)	209862	10/19/2016	Autoinjector
Zimhi (5 mg)	212854	04/29/2021	Pre-filled Syringe
Kloxxado (8 mg)	212045	10/15/2021	Nasal Spray

Source: Created by Reviewer

Appendix 2: Summary of Clinical Data for Use of Naloxone HCl in Adolescent Patients Provided in NDA 215457

Study Type	Inclusion Rationale	Age (yr) and/or Weight (kg)	Naloxone HCl Dose	Comment / Notable Findings	Publication Year	Reference
Randomized Controlled Trial	Safety	13 – 34 yr	Initial IV bolus of 5.4 mg/kg followed by IV infusion of 4 mg/kg/hr	• Acute spinal cord injury, N=154 • Randomized to methylprednisolone, naloxone HCl, or placebo • No evidence of naloxone HCl efficacy in acute spinal cord injury • Safety observations not reported for naloxone HCl	1990	(Bracken MB, et al, 1990)
Medical Record Review	Safety	13 – 17 yr	IV dose unknown	• Intentional ingestion of methadone (n=5) or buprenorphine (n=1) • 4/6 received IV naloxone HCl (bolus ± infusion) • Hospital stay 2 days for the 4 patients who received naloxone HCl vs 2 or 7 days for the 2 patients who didn't receive naloxone HCl • No fatalities	2011	(Martin & Rocque, 2011)
Medical Record Review	Safety	0.5 – 16 yr	Initial IV bolus of 3 to 10 mg followed by IV infusion if needed ranging from 2 to 30 mg/hr	• Pediatric patients with clonidine toxicity, N=52 (all patients received initial IV bolus and 21/52 of those received 10 mg as initial IV bolus; 35/52 received IV infusion) • No AEs following administration of naloxone HCl at any dose	2018	(Seger & Loden, 2018)

Case Report	Safety	1 – 12 yr	IV dose unknown	• Fentanyl used as anesthesia for facial laceration repair with naloxone HCl required for apnea in 3/2000 cases • All patients discharged without further complications	1985	(Billmire DA, et al, 1985)
Case Report	Safety	26 yr / 54 kg	10 mg (2 mg IN plus 8 mg IV)	• Suspected IV heroin/carfentanil overdose • No reported AEs • Weight consistent with 50th percentile for ~13-yr old female using NHANES or a 16-yr old female using CDC growth chart	2019	(Bardsley R, 2019)

Source: Response to Information Request, eCTD# 0009, December 1, 2021

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JOHN J ALEXANDER
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HUMAN FACTORS STUDY REPORT REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 26, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215457
Drug Constituent Name and Strength	Naloxone hydrochloride injection, 10 mg
Product Type:	Combination Product (Drug-Device)
Device Constituent:	Autoinjector
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Kaleo, Inc.
FDA Received Date:	August 31, 2021, December 29, 2021, January 11, 2022
OSE RCM #:	2021-1732
DMEPA 1 Human Factors Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study reports submitted under NDA 215457 for naloxone hydrochloride (HCl) injection, 10 mg.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed autoinjector device constituent part (b) (4) [redacted] The proposed autoinjector is similar to the Applicant's currently approved Evzio (naloxone HCl injection) 2 mg (NDA 209862), which is discontinued due to business reasons. Unlike Evzio, the proposed autoinjector does not have the electronic prompt system (EPS). The U.S. Department of Defense (DoD) requested the Applicant develop the proposed autoinjector without the EPS. The carton will consist of ten naloxone HCl Injection, Autoinjector, 10 mg (NAI 10 mg), prescribing information and instructions for use (IFU). The autoinjector will come in an outer case. Images of the autoinjector and the outer case are depicted in Figure 1 below. For additional product information, please see Table 5 in Appendix A.

Figure 1. Naloxone HCl Injection, Autoinjector

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On July 29, 2020, the Applicant submitted their HF validation study protocol with emergency medical services (EMS) personnel and law enforcement officer (LEO) as the intended users under their IND 112292 for Agency feedback. We reviewed the protocol and provided recommendations to the Applicant.[a]
- On December 23, 2020, the Applicant submitted HF validation study protocol with military personnel as the intended users under their IND 112292 for Agency feedback. We reviewed the protocol and provided recommendations to the Applicant.[b]
- On August 31, 2021, the Applicant submitted HF validation study results reports for EMS, LEO and Military Personnel under NDA 215457, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

[a] Johnson, C. Human Factors Validation Study Protocol Review for naloxone hydrochloride injection (IND 112292). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 22. RCM No.: 2020-1417.

[b] Flint, J. Human Factors Validation Study Protocol Review for naloxone hydrochloride injection (IND 112292). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 16. RCM No.: 2020-2713.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study designs, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface has been optimized to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGNS

Table 2 presents a summary of the HF validation study designs.

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	**Details:** Emergency Medical Services (EMS) personnel and Law Enforcement Officer (LEO)	**Details:** Military Personnel
Participants	30 EMS personnel • n = 15 with Evzio and/or Auvi-Q experience (participants in the experienced group were provided an Auvi-Q trainer and Auvi-Q package insert to take home and returned a week later for the simulated use part of the study. Auvi-Q epinephrine autoinjector uses the same device platform and similar EPS as Evzio. Evzio and Auvi-Q were chosen to determine whether the removal of the EPS introduce new issues including the potential for negative transfer from Evzio and Auvi-Q) • n = 15 without Evzio and/or Auvi-Q experience 30 LEO • n = 15 with Evzio and/or Auvi-Q experience (participants in the experienced group were provided an Auvi-Q trainer and Auvi-Q package insert to take home and returned a	15 Military personnel familiar with Mission Oriented Protective Posture (MOPP) Level 4 protective equipment

	week later for the simulated use part of the study. Auvi-Q epinephrine autoinjector uses the same device platform and similar EPS as Evzio. Evzio and Auvi-Q were chosen to determine whether the removal of the EPS introduce new issues including the potential for negative transfer from Evzio and Auvi-Q) • n = 15 without Evzio and/or Auvi-Q experience	
Training	No training on the use of NAI 10 mg was provided to test participants.	Participants were trained on device use prior to simulated use scenario as this is standard practice for the military. Training was conducted either one-on-one or in small groups and lasted approximately 30 minutes. The content of training was analogous to real world training, based on the device, device label, and instructions for use (IFU), and developed by the military trainer. Training occurred one week prior to the simulated use scenarios to approximate training decay.
Test Environment	Participant test sessions were conducted in a research facility, where one area was setup to reflect a storage room or closet where the LEO/EMS participant could "pack their bag" at the start of their shift or prior to responding to a scene. The session room was configured to simulate a sports bar/recreational area with a couple patrons in the vicinity. Lighting, sound, and temperature were what would be expected from a sports bar/recreational area and included pop/rock music playing in the	Participant test sessions were conducted at the Human Factors MD research facility, in rooms where the participant packed their protective mask carrier and donned MOPP Level 4 protective equipment, and an area setup for the simulated scenes with hot zone and warm zone. In the hot zone scene, there were multiple causalities, furniture and debris on the ground, red flashing lights, fog, and background noises. In the warm zone scene, there were peripheral flashing lighting and background noises.

	background (approximately 75 decibels (dB) with the only lighting coming from a rotating ceiling-mounted disco ball displaying colored lights around the room (i.e., there was no overhead room lighting during the simulation). In addition, time urgency, lack of assistance, and stress inducers were incorporated to better simulate an emergency. The beeping tone played through speakers and increased in frequency and volume over a 2-minute time span during the use scenario which was a stress inducer. Storage area: (b) (4) <u>Session room setup:</u> (b) (4)	<u>Hot zone:</u> (b) (4) Warm zone: (b) (4)

Sequence of Study	• Simulated-use scenario • Root cause analysis (the moderator carried out a root cause analysis to identify what contributing factors may have been responsible for any observed and/or reported use issues or errors) • Knowledge task questions • Root cause analysis	• Scenario 1: The participant needs to carry out a buddy administration of naloxone HCL 10 mg to an affected soldier (using the affected soldier's NAI 10 mg). • Scenario 2: The participant has been "contaminated" and needs to self-administer naloxone HCL 10 mg to him/herself. • Root cause analysis • Knowledge based questions

2.1.1 METHODOLOGY DISCUSSION

Our review of the HF validation study methodology finds that the Applicant did not assess the task related to administering a second dose in the EMS and LEO HF validation study, as we recommended in our HF Validation Study Protocol Advice Letter.[c] The Applicant provided a rationale for not including a scenario to assess the task related to administering a second dose. Per the Applicant, packing of multiple doses for one patient should not be necessary given the amount of naloxone HCL (10 mg) in a single dose. On December 27, 2021, we issued an Information Request (IR) to clarify the intent of the IFU statement, "If symptoms return, additional naloxone may be administered." The Applicant stated that after the initial use of NAI 10 mg, emergency medical treatment should be sought and if the patient exhibits renarcotization, additional naloxone may be administered. The Applicant also stated that because alternative forms of naloxone such as a vial of naloxone HCl injection or an intranasal naloxone product are typically available to first responders (e.g., EMS, LEO, military personnel), the proposed language is provided to instruct the user to use whatever additional naloxone is available if renarcotization occurs. Our review finds that based on the above considerations, we find the Applicant's rationale for not including a task to administer a second dose acceptable.

Additionally, our review of the HF validation study methodology notes that the Applicant gave all participants in the EMS and LEO experienced groups, the Auvi-Q trainer and Auvi-Q package insert to take home and return a week later for the simulated use part of the study. The Auvi-Q trainer was given due to the discontinuation of Evzio from the market and low incidence rate of EMS and LEO having experience with Auvi-Q. These participants were considered experienced for the purposes of the HF validation study. However, we

[c] White, T. Human Factors Validation Study Protocol Advice Letter for naloxone hydrochloride injection (IND 112292). Silver Spring (MD): FDA, CDER, OND, DAAP (US); 2020 SEP 25. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8059a67e&_afrRedirect=308742766923746

noted that the Applicant did not provide details on whether the EMS and LEO participants used the Auvi-Q trainer during the week prior to the simulated use scenario. On January 7, 2022, we issued an IR to the Applicant to obtain details on how many users actually used the Auvi-Q trainer prior to their study session. On January 11, 2022, the Applicant responded that all participants in the experienced user groups of LEO and EMS personnel interacted with the Auvi-Q trainer during the week prior to the simulated use scenario. Based on the information available that Evzio product has been discontinued from the market and the low incidence rate of EMS and LEO having experience with Auvi-Q, we find the Applicant's rationale for providing an Auvi-Q trainer to the EMS and LEO in the 'experienced' groups a week before their study session acceptable.

3 RESULTS AND ANALYSES

Tables 3 and 4 describe the study results, the Applicant's analyses of the results, and DMEPA 1's analyses and recommendations.

3.1 EMERGENCY MEDICAL SERVICE (EMS) PERSONNEL AND LAW ENFORCMENT OFFICER (LEO) HF VALIDATION STUDY RESULTS

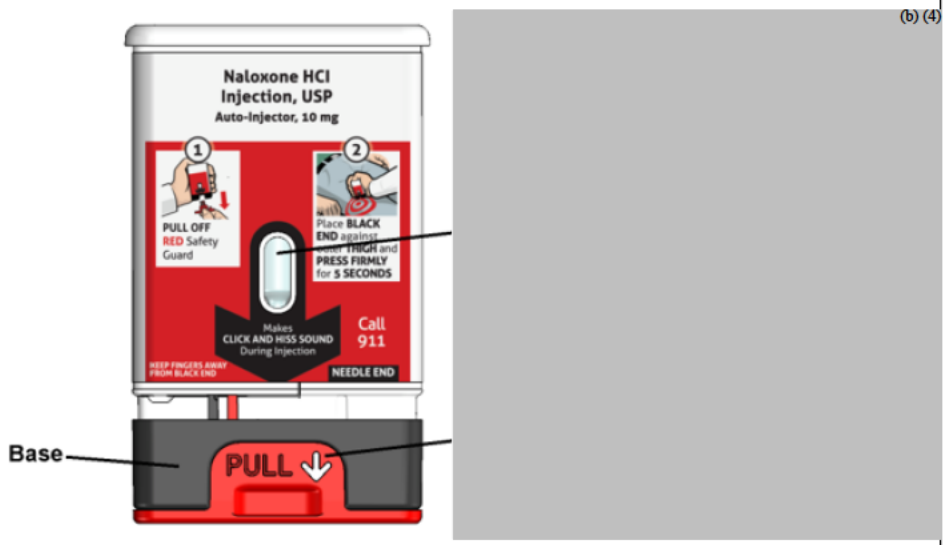
We note that there were use difficulties with the use of the autoinjector assessed during the EMS personnel and LEO HF validation study. Table 3 describes these use difficulties.

Table 3: Identified Issues and DMEPA's Findings – EMS Personnel and LEO HF Validation Study

Please note the following acronyms below.

FRU – naive first responders (EMS including firefighter, EMT, paramedic)
FRT – experienced first responders (EMS including firefighter, EMT, paramedic)
LEOU – naïve law enforcement officers
LEOT – experienced law enforcement officers

	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the task to "Pull NAI from the outer case", there were 2 use difficulties (1 naïve EMS and 1 naïve LEO). FRU-01 was pulling on the purple part of the outer case, not realizing that he needed to hold on to the exposed white part of the device. He also reported that he interpreted the images in instructions for use (IFU) Figure A to be a before and after picture, indicating that he thought the picture on the right was what the device would look like when ready to use. LEOU-06 had initial difficulty because he was using his full grip on the outer case of the device. The Applicant's root cause analysis indicated that participants placed a firm grip on the outer case of the device which likely compressed the outer case against the device making it hard to remove the outer case. The Applicant also stated that a potential contributing factor	Based on the URRA, if this task is omitted or not performed correctly there is risk of a delay in the treatment with naloxone or death because of the opioid overdose if no injection. Our review of the study results identified subjective feedback that indicated that participants placed a firm grip on the outer case of the device and one participant misinterpreted the images in IFU figure A to be a before and after picture and thought the picture on the right was what the device would look like when ready to use.

	may have been that the cut-out in the outer case at the top (i.e., for finger placement) may not have been apparent or prominent enough to capture the participants' attention. The Applicant stated both participants knew that removing the outer case was required as the first step in the NAI injection process and both participants understood that the device is removed from the outer case by pulling up on the device suggesting the labeling on the device and in the IFU is adequate. Additionally, the Applicant stated that given the functionality of the outer case and the fact that the two participants were still able to complete the task in a timely manner, the Applicant concluded that additional risk mitigation measures are not necessary, and the resulting low residual risk associated with these use difficulties is acceptable.	NALOXONE AUTO-INJECTOR, 10 mg Outer Case  We note that although these two participants had difficulty pulling the NAI outer case, they were still able to successfully administer the injection in less than 1 minute. The Applicant stated that the total time it took to administer a successful injection starting from when these participants first tried to remove the outer case to lifting the device from the leg after completing the injection was less than 1 minute (54 seconds and 20 seconds) respectively. Additionally, the Applicant stated that since this is an emergency use device, the outer case is designed to prevent premature device activation or exposure and the tight fit helps ensure the outer case is not accidentally dislodged or removed. We reached out to our Center for Devices and Radiological Health (CDRH) colleagues. They confirmed that the proposed NAI outer case removal force is comparable to other approved similar autoinjectors: Evzio 2 mg and Evzio 0.4 mg. Therefore, CDRH found the proposed NAI outer case removal force acceptable.

		Based on the subjective feedback and our review of the labels and labeling (user interface, etc.), we note that the IFU does not include a figure that depicts what the device looks like intact before the user pulls the NAI from the outer case. **We provide our recommendation in Table A to address this concern.** We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
2.	For the task to "Pull off the red safety guard", there were 2 use difficulties (1 experienced EMS and 1 experienced LEO). LEOT-05 noted that the red safety guard was tougher than he expected to pull off. FRT-07 was afraid to pull too hard to get the red safety guard off. The Applicant's root cause analysis indicated that the red safety guard is firmly positioned in the device which is the most likely contributing factor for this observation. The Applicant stated both participants knew that removing the red safety guard was the second step in the NAI injection process and both participants had experience using the Auvi-Q trainer and understood how to remove the red safety guard. Additionally, the Applicant stated that given the functionality of the red safety guard and the fact that the two participants were still able to complete the task in a timely manner, the Applicant concluded that additional risk mitigation measures are not necessary, and the resulting low residual risk associated with these use difficulties is acceptable.	Based on the URRA, if this task is omitted or not performed correctly there is risk of a delay in the treatment with naloxone or death because of the opioid overdose if no injection. Our review of the study results identified subjective feedback that indicated that the participants had difficulty pulling off the red safety guard as it is made to fit tightly and requires a user to pull firmly to remove. One participant stated that he cannot imagine the tightness keeping anyone from removing the safety guard as needed in a high stress situation, given the fact that he was able to remove the red safety guard and successfully administer the injection in 16 seconds. The Applicant stated that the total time it took to administer a successful injection starting from when these participants removed the outer case to lifting the device from the victim's leg after completing the injection was less than 1 minute (18 seconds and 16 seconds) respectively. Additionally, the Applicant stated that as an emergency use device, the red safety guard is designed to fit tightly to prevent it from being accidentally dislodged or removed before intended which could result in the device being prematurely activated. Also, the tight fit of the red safety guard helps ensure the protective barrier over the needle by the sheath is maintained. Furthermore, the Applicant stated, the force necessary to pull off the red safety guard strikes a necessary balance between too high and too low. The Applicant also stated that the force necessary is high enough to prevent accidental safety guard removal and possible, subsequent premature device activation while also low enough to allow users with less strength to complete the injection process when needed. Lastly, the Applicant stated

these use difficulties did not prevent either participant from administering a successful injection within less than a minute.

We reached out to our CDRH colleagues. They confirmed that the proposed red safety guard removal force is comparable to other approved similar autoinjectors: Evzio 2 mg and Evzio 0.4 mg. Therefore, CDRH found the proposed red safety guard removal force acceptable.

Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 2 contains text and illustration (see image below) on pulling off the red safety guard. Additionally, Step 2 also states to note that the red safety guard is made to fit tightly and to pull firmly to remove. The recommended grip position is also illustrated in Step 1 of the on-device label.

Step 2.

Pull off the **Red** safety guard. See Figure C.

To reduce the chance of an accidental injection, **do not** touch the **Black** base of the auto-injector, which is where the needle comes out.

Figure C – Remove Red Safety Guard

Note: The **Red** safety guard is made to fit tightly. **Pull firmly to remove.**

Do not replace the **Red** safety guard after it is removed.

		 We have not identified additional changes to the user interface to further reduce the risks associated with these use difficulties. We find that the residual risk in this case is acceptable.
3.	For the task to "Hold in place for at least 5 seconds", there were 12 use difficulties (2 experienced EMS, 5 naïve EMS, 3 experienced LEO and 2 naïve LEO). Participants held for less than 5 seconds as they thought hiss and click sound represented the medication being delivered and completion of the injection. Eleven participants reported counting to the full 5 seconds in their head.	Based on the URRA, if this task is omitted or not performed correctly there is risk of less than full dose given, a delay in the treatment with naloxone or death because of the opioid overdose if no dose given. On December 27, 2021, we issued an information request (IR) to the Applicant to obtain the average injection time for the NAI devices. On December 29, 2021, the Applicant responded that the mean dispensing time of the NAI 10 mg devices was 293 ± 114 milliseconds (0.293 ± 0.114 seconds) with a minimum of 218 milliseconds (0.218 seconds) and maximum of 727 milliseconds (0.727 seconds).

	The Applicant's root cause analysis indicated the contributing factor for these use difficulties is that people count too quickly especially during an emergency situation and the body's automatic response to the mechanical sounds emitted from the device as part of the activation process (i.e., click and hiss) is to lift the device from the injection site. The Applicant stated that a hold time of 5 seconds was originally chosen for the NAI IFU and device labeling to allow for a time buffer (safety factor) to increase the chance that the device is held for at least 1 second thereby ensuring completion of naloxone administration. As it is known that people may rush counting or underestimate short lengths of time, especially during an emergency use scenario. Additionally, the Applicant stated that the naloxone HCL 10 mg dose is delivered in less than 1 second and all 60 participants in this study held the device in position for longer than 1 second (average 5.6 seconds, minimum 3 seconds, maximum 10 seconds). Therefore, if this were an actual opioid emergency, all victims would have received a full, clinically meaningful dose of naloxone in all cases. The Applicant concluded that additional risk mitigation measures are not necessary, and the resulting low residual risk associated with these use difficulties is acceptable.	Our review of the study results identified subjective feedback that indicated that the participants misinterpreted the hiss and click sound and thought that the sounds represented the medication being delivered and completion of the injection. However, these use difficulties did not prevent any participant from administering a successful injection. All 12 participants with use difficulties held the device in place for at least 1 second (average 4 seconds, minimum 3 seconds, maximum 4 seconds) and therefore completed the injection task and administered a full dose. Based on the subjective feedback and our review of the labels and labeling (user interface, etc.), we note that the IFU does not clearly specify the meaning of the click and hiss sounds. As such, our review of the IFU finds that meaning of the click and hiss sounds can be further clarified. **We provide our recommendation in Table A to address this concern.** We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
4.	For the knowledge task question, "What should the drug look like?", there was 1 partially correct answer (experienced EMS). The Applicant stated that answers are partially correct when the participant provides some, but not all the information necessary to demonstrate a complete and accurate understanding of the information provided in the labeling, as well as any implications for the use of the product and patient safety.	Based on the URRA, if this task is omitted or not performed correctly there is risk of administering degraded drug product that may lead to less effective dose. Our review of the study results indicates that the root cause analysis was incomplete because the Applicant did not identify why the participant took a long time to find the information in the IFU and they did not specify if the participant was able to find the information in the IFU.

	FRT-08 took a long time to find the information that the drug is clear. The Applicant stated that the information was probably not conspicuous enough for the participant to find immediately but does not suggest the IFU is inadequate in presenting this information. The Applicant did not propose any mitigation strategies for this use error.	Our review of the labels and labeling (user interface, etc.) finds that the IFU includes information on what the drug should look like in the autoinjector. We have not identified additional changes to the user interface to further reduce the risks associated with this use error. We find that the residual risk in this case is acceptable.

3.2 MILITARY PERSONNEL HF VALIDATION STUDY RESULTS

We note that there were use difficulties with the use of the autoinjector assessed during the Military HF validation study. Table 4 describes these use difficulties.

Table 4: Identified Issues and DMEPA's Findings – Military personnel HF Validation Study

	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the task to "Pull off the red safety guard", there was 1 use difficulty in the self-administration scenario. P11 could not get a good grip on the red safety guard due to the MOPP level 4 gloves he was wearing. The Applicant's root cause analysis indicated that the red safety guard is firmly positioned in the device which may result in some difficulty when attempting to grip while wearing thick chemical gloves (as worn with MOPP Level 4 protective equipment). The Applicant stated the participant knew that removing the red safety guard is the second step in the NAI injection	Based on the URRA, if this task is omitted or not performed correctly there is risk of a delay in the treatment with naloxone or death because of the opioid overdose if no injection. Our review of the study results identified subjective feedback that indicated that the participant had difficulty pulling off the red safety guard as the MOPP level 4 gloves he was wearing made it difficult to pull the red safety guard off. The Applicant stated that the total time it took to administer the successful injection starting from when the participant removed the outer case to lifting the device from his leg after completing the injection was 37 seconds and the participant was still able to complete the injection and administer the full dose.

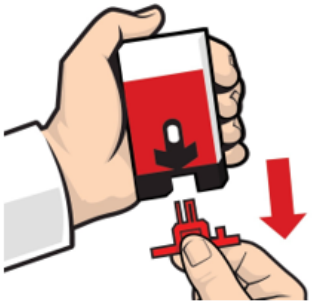
	process and understood how to remove the red safety guard. The Applicant also stated that the intended military user group will have required routine training for NAI 10 mg to ensure familiarity and ease in using NAI 10 mg, even in MOPP Level 4 protective equipment, thus mitigating this risk further. Given the functionality of the red safety guard and the fact that the participant was still able to complete the task in a timely manner, the Applicant concluded that additional risk mitigation measures are not necessary, and the resulting low residual risk associated with this use difficulty is acceptable.	Additionally, the Applicant stated that as an emergency use device, the red safety guard is designed to fit tightly to prevent it from being accidentally dislodged or removed before intended which could result in the device being prematurely activated. Also, the tight fit of the red safety guard helps ensure the protective barrier over the needle by the sheath is maintained. Furthermore, the Applicant stated, the force necessary to pull off the red safety guard strikes a necessary balance between too high and too low. The Applicant also stated that the force necessary is high enough to prevent accidental safety guard removal and possible, subsequent premature device activation while also low enough to allow users with less strength to complete the injection process when needed. Lastly, the Applicant stated this use difficulty did not prevent the participant from administering a successful injection within less than a minute. We reached out to our CDRH colleagues. They confirmed that the proposed red safety guard removal force is comparable to other approved similar autoinjectors: Evzio 2 mg and Evzio 0.4 mg. Therefore, CDRH found the proposed red safety guard removal force acceptable. Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 2 contains text and illustration (see image below) on pulling off the red safety guard. Additionally, Step 2 also states to note that the Red safety guard is made to fit tightly and to pull firmly to remove. The recommended grip position is also illustrated in Step 1 of the on-device label.

Step 2.

Pull off the **Red** safety guard. See Figure C.

To reduce the chance of an accidental injection, **do not** touch the **Black** base of the auto-injector, which is where the needle comes out.

Figure C – Remove Red Safety Guard



Note: The **Red** safety guard is made to fit tightly. **Pull firmly to remove.**

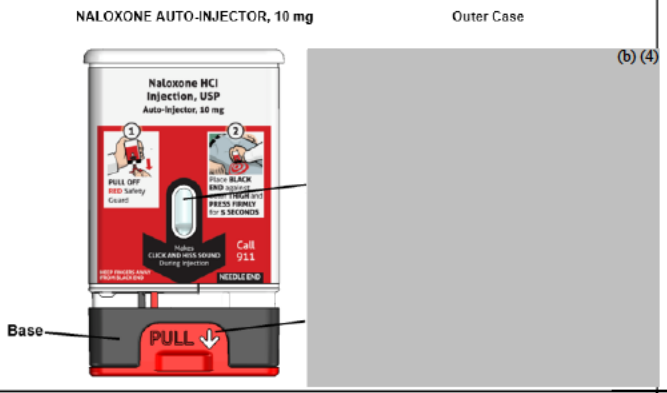
Do not replace the **Red** safety guard after it is removed.

		 We also acknowledge that the intended users need to wear the chemical gloves with MOPP level 4 protective equipment. Although the participant had difficulty, he was able to complete this task and administer the full dose in a timely manner (37 seconds). As such, we find this use difficulty does not require any further mitigation. We find that the residual risk in this case is acceptable.
2.	For the task to "Hold in place for at least 5 seconds", there were 2 use difficulties in the buddy administration scenario and 1 use difficulty in the self-administration scenario. P05 stated that he forgot. P13 held for less than 5 seconds in both scenarios. He was focused on if this had been a real situation and the need	Based on the URRA, if this task is omitted or not performed correctly there is risk of less than full dose given, a delay in the treatment with naloxone or death because of the opioid overdose if no dose given. On December 27, 2021, we issued an information request (IR) to the Applicant to obtain the average injection time for the NAI devices. On December 29, 2021, the Applicant responded that the mean dispensing time of the NAI 10 mg devices was 293 ± 114 milliseconds (0.293 ± 0.114 seconds)

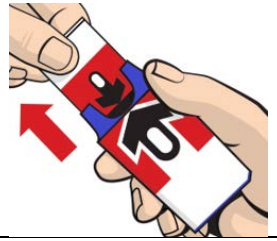
	to remove his fellow soldier and himself from the environment as quickly as possible. This participant also noted that in real circumstances, had his buddy soldier been conscious, he would have asked the comrade to hold the device in place while he dragged him out of the area. The Applicant's root cause analysis indicated the contributing factor for these use difficulties to be that people count too quickly especially during an emergency situation and the need to follow standard military procedure to quickly evacuate a harmful environment/situation. The Applicant stated that a hold time of 5 seconds was originally chosen for the NAI IFU and device labeling to allow for a time buffer (safety factor) to increase the chance that the device is held for at least 1 second thereby ensuring completion of naloxone administration. As it is known that people may rush counting or underestimate short lengths of time, especially during an emergency use scenario. Additionally, the Applicant stated that the naloxone HCL 10 mg dose is delivered in less than 1 second and all 15 participants in this study held the device in position for longer than 1 second (minimum 2 seconds, maximum 15 seconds). Therefore, if this were an actual opioid emergency, all victims would have received a full, clinically meaningful dose of naloxone in all cases. The Applicant concluded that additional risk mitigation measures are not necessary, and the resulting low residual risk associated with these use difficulties is acceptable.	with a minimum of 218 milliseconds (0.218 seconds) and maximum of 727 milliseconds (0.727 seconds). Although we did not identify any subjective feedback on the use issues for military personnel user group, our review of the study results with EMS personnel and LEO identified subjective feedback that indicated that the participants misinterpreted hiss and click sound and thought that hiss and click represented the medication being delivered and completion of the injection. However, these use difficulties did not prevent any participant from administering a successful injection. Both participants with use difficulties held for at least 1 second (average 3 seconds, minimum 2 seconds, maximum 5 seconds) and therefore administered full dose. Based on the subjective feedback and our review of the labels and labeling (user interface, etc.), we note that the IFU does not clearly specify the meaning of the click and hiss sounds. As such, our review of the IFU finds that meaning of the click and hiss sounds can be further clarified. **We provide our recommendation in Table A to address this concern.** We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

3.3 INSTRUCTIONS FOR USE

Table A below includes the identified medication error issues with the submitted instructions for use (IFU), our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table A: Identified Issues and Recommendations for Kaleo, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Instructions for Use (IFU)			
1.	The IFU does not include a figure that depicts what the device looks like intact before the user pulls the naloxone autoinjector (NAI) from the outer case.	We are concerned if the user does not pull the NAI from the outer case, there is risk of a delay in the treatment with naloxone or death because of opioid overdose if no injection is given. The human factors (HF) validation study identified subjective feedback that indicated the participant misinterpreted the images in IFU figure A to be a before and after picture and thought the picture on the right was what the device would look like when ready to use. 	We recommend revising the IFU to add a figure prior to figure A that depicts what the device looks like intact before the user pulls the NAI from the outer case.
2.	The IFU does not clearly specify the meaning of the click and hiss sound that is heard after user presses	We are concerned if the user does not hold the NAI in place for at least 5 seconds, there is risk of less than full dose given, a delay in the treatment with naloxone or death because of opioid overdose if no dose is given. The HF validation	We recommend revising the IFU to clearly specify the meaning of click and hiss sound that is heard after user presses the NAI against the injection site.

	the NAI against the injection site.	study identified subjective feedback that indicated that the participants misinterpreted the click and hiss sound to mean that the medication had been delivered and the injection was complete.	
3.	There is inconsistency with respect to the color of the NAI outer case. For example, the color of the NAI outer case image in Figure B is blue. However, the NAI samples provided and the color of the NAI outer case image in Figure A is purple. The color image in Figure B is not consistent with the color of the outer case image in Figure A and samples reviewed. <u>Image in figure A:</u>	Inconsistency between the color of the NAI outer case image in figure B and the NAI samples provided and the color of the NAI outer case image in Figure A may lead to confusion.	Ensure the NAI image and colors in the IFU align with the to-be-marketed product.

	(b) (4) Image in figure B: 		

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation studies demonstrated several use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use difficulties. Above, we have provided recommendations in Table A for the Applicant. We ask that the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) convey Table A in its entirety to the Applicant. These changes can be implemented without submitting additional HF validation testing data for Agency review.

4.1 RECOMMENDATIONS FOR KALEO, INC.

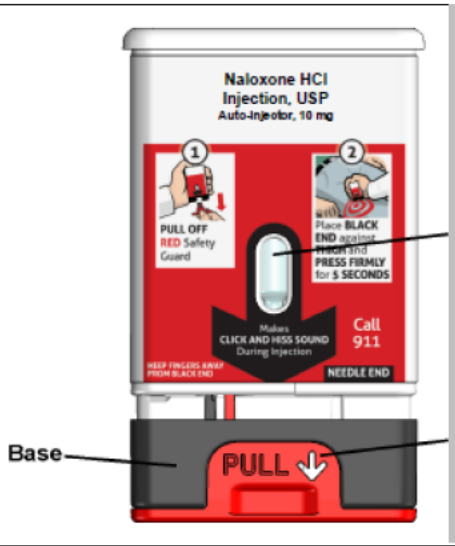
Our evaluation of the results of your human factors (HF) validation studies indicates that there are additional mitigations that can be implemented to address use difficulties that occurred with critical tasks. We provide recommendations in Table A and we recommend that you implement these recommendations and submit the revised labels and labeling for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for naloxone hydrochloride that Kaleo, Inc. submitted on August 31, 2021.

Table 5. Relevant Product Information	
Initial Approval Date	October 19, 2016 (2 mg/0.4 mL discontinued) April 3, 2020 (0.4 mg/0.4 mL discontinued)
Therapeutic Drug Class or New Drug Class	Opioid antagonist
Active Ingredient (Drug or Biologic)	Naloxone hydrochloride
Indication	10 mg/0.4 mL (proposed): (b) (4)
Route of Administration	intramuscular and subcutaneous
Dosage Form	injection
Strength	10 mg/0.4 mL
Dose and Frequency	10 mg injected into thigh. If the patient relapses into respiratory or central nervous system depression, additional naloxone hydrochloride may be administered.
How Supplied	Package containing ten naloxone hydrochloride autoinjectors
Storage	(b) (4)
Container Closure/Device Constituent	Autoinjector

	 (b) (4)
Intended Users	Emergency Medical Services Personnel, Law Enforcement Officer, and Military personnel (e.g., military members and government civilians)
Intended Use Environment	Anywhere (indoor or outdoor, day or evening)

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On September 22, 2021, we searched the L:drive and AIMS using the terms, NDA 215457, IND 112292 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified two previous reviews[d,e], and we considered our previous recommendations to see if they are applicable for this current review.

[d] Johnson, C. Human Factors Validation Study Protocol Review for naloxone hydrochloride injection (IND 112292). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 22. RCM No.: 2020-1417.

[e] Flint, J. Human Factors Validation Study Protocol Review for naloxone hydrochloride injection (IND 112292). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 16. RCM No.: 2020-2713.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

Use-related risk analysis (URRA) can be accessible in EDR via:
\\CDSESUB1\evsprod\nda215457\0001\m3\32-body-data\32p-drug-prod\naloxone-auto-injector\32p7-cont-closure-sys\urra-rpt-dvl-0051.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF validation study results report with Emergency Medical Services (EMS) personnel and law enforcement officer (LEO) user group can be accessible in EDR via:
\\CDSESUB1\evsprod\nda215457\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\opiod-exp\5354-other-stud-rep\ka-1000se-002\ka-1000se-002.pdf

The HF validation study results report with military personnel user group can be accessible in EDR via: \\CDSESUB1\evsprod\nda215457\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\opiod-exp\5354-other-stud-rep\ka-1001se-002\ka-1001se-002.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On December 27, 2021, we issued an Information Request (IR) to:

- obtain average injection completion time for the autoinjectors
- obtain clarification on intent of the IFU statement “If symptoms return, additional naloxone may be administered.”
- obtain clinical impact for all user errors listed in the URRA.

The Applicant provided an acceptable response on December 29, 2021 that can be accessible in EDR via:

\\CDSESUB1\evsprod\nda215457\0011\m1\us\111-info-amend\resp-req-inf.pdf

On January 7, 2022, we issued an IR to:

- obtain clarification on why Evzio 0.4 mg and Evzio 2 mg have been discontinued.
- obtain information on whether the users actually used the Auvi-Q trainer that were provided to the users in the experienced group.

The Applicant provided an acceptable response on January 11, 2022 that can be accessible in EDR via:

\\CDSESUB1\evsprod\nda215457\0014\m1\us\111-info-amend\resp-req-inf.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following naloxone hydrochloride labels and labeling submitted by Kaleo, Inc.

- Instructions for Use (Image not shown) received on August 31, 2021, available from \\CDSESUB1\evsprod\nda215457\0001\m1\us\114-label\1141-draft-label\proposed-ifu.docx

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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AVANI BHALODIA
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: January 11, 2022 **Date consulted:** September 9, 2021

From: Jean Limpert, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

To: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Drug: Naloxone Auto-Injector 10 mg

NDA: 215457

Applicant: Kaleo, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indications: (b) (4)

Materials
Reviewed:

- DPMH consult request dated September 9, 2021, DARRTS Reference ID 4855116
- Applicant's submitted background package and proposed labeling for NDA 215457
- Applicant's response to the DPMH Information Request (IR) dated October 1, 2020
- DPMH labeling review for Zimhi (naloxone hydrochloride) injection for intramuscular or subcutaneous use, NDA 212854, October 23, 2020, Miriam Dinatale, DO, Team Leader, DARRTS Reference ID 4691494.[1]
- DPMH review of Narcan (naloxone) Nasal Spray, NDA 208411, September 28, 2015, Suchitra Balakrishnan, MD, PhD. DARRTS reference ID 3834852.[2]

Consult Question: "We are also requesting a MHT consult to assist us in reviewing the label."

INTRODUCTION AND BACKGROUND

On August 31, 2021, Kaleo, Inc, submitted a 505(b)2 new drug application (NDA) for approval of a 10 mg strength of naloxone auto-injector (b) (4) according to the proposed indications described above.

The formulation of naloxone auto-injector 10 mg is identical to the approved naloxone auto-injector in the 0.4 and 2 mg formulations except it is formulated to a higher drug concentration of 25 mg/mL. The applicant is relying on the Agency's previous findings of safety and efficacy for NARCAN (naloxone hydrochloride; NDA 016636) and their EVZIO (autoinjector) (naloxone hydrochloride; NDA 20982). On September 9, 2021, DAAP consulted DPMH to assist with the Pregnancy and Lactation Rule (PLLR) subsections of labeling.

Regulatory History

- Naloxone, as an active ingredient, has been approved since 1971 and is available as an auto-injector, intranasal spray, and injection for the emergency treatment of known or suspected opioid overdose. Naloxone is also approved as a combination drug with buprenorphine for the treatment of opioid use disorder.
- Kaleo's EVZIO single-use auto-injector is approved in two doses: 0.4 mg (approved in 2014) and 2 mg (approved in 2016). Both strengths of the auto-injector were discontinued but not for reasons of safety or efficacy.[3]
- On April 2, 2021, FDA granted this NDA Fast Track Designation for the treatment of ultra-potent opioid exposure in adults.
- On September 16, 2021, DPMH sent an IR to the applicant to request published literature and pharmacovigilance information for the PLLR review. On October 1, 2021, the applicant submitted their response.

[1] The Zimhi review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[2] The Narcan review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[3] Clinical Pharmacology Filing Review for NDA 215457, dated 10/4/2021, DARRTS Reference ID 4866989.

- DPMH completed a recent review for another naloxone hydrochloride injection in October 2020. For labeling (b) (4) DPMH did not recommend (b) (4) For labeling (b) (4) DPMH did not recommend (b) (4) For full details, the reader is referred to the referenced review.[4]

Drug Characteristics[5]

- Drug class: opioid antagonist
- Mechanism of action: naloxone antagonizes the opioid effect by competing for the same receptor sites
- Dose and administration: Administered as a single 10 mg dose of naloxone in a 0.4 mL solution. If the patient relapses into respiratory or central nervous system depression, additional naloxone hydrochloride may be administered. A maximum dose is not specified.
- Molecular weight: 327 Daltons[6]
- Half-life: 1.5 hours
- Plasma protein binding occurs but is relatively weak

Opioid Overdose and Pregnancy

- From 1999 to 2019, overdose deaths involving opioids increased over 500%. The majority of overdose deaths are attributed to synthetic opioids.[7] Use of ultra-potent opioids, including synthetic opioids, can result in rapid onset of central nervous system and respiratory depression and shorten the window for effective intervention.
- It is recommended that people who receive naloxone are observed constantly until emergency care arrives and monitored for another two hours after the last dose to make sure changes in breathing and respiratory depression do not recur.[8]
- Several states have identified opioid-related overdoses as a contributor in 11-20% cases of pregnancy-associated deaths.[9]
- Opioid use disorder during pregnancy has been linked to fetal growth restriction, abruption placentae, fetal death, and preterm labor.[10,11]
- Medications for opioid use disorder during pregnancy include methadone or buprenorphine, the latter of which is also approved in combination with naloxone.

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[4] DPMH labeling review for Zimhi (naloxone hydrochloride) injection for intramuscular or subcutaneous use, NDA 212854, October 23, 2020, Miriam Dinatale, DO, Team Leader, DARRTS Reference ID 4691494.[4]
[5] Applicant's proposed labeling for Naloxone Auto-Injector NDA 214457
[6] Naloxone | C19H21NO4 - PubChem (nih.gov)
[7] https://drugabusestatistics.org/opioid-epidemic/
[8] https://www.drugabuse.gov/publications/drugfacts/naloxone
[9] Schiff DM, Nielsen T, Terplan M, Hood M, Bernson D, Diop H, Bharel M, Wilens TE, LaRochelle M, Walley AY, Land T. Fatal and Nonfatal Overdose Among Pregnant and Postpartum Women in Massachusetts. Obstet Gynecol. 2018 Aug;132(2):466-474. doi: 10.1097/AOG.0000000000002734.
[10] https://www.cdc.gov/pregnancy/opioids/basics.html
[11] Nguyen L, Lander LR, O'Grady KE, Marshalek PJ, Schmidt A, Kelly AK, Jones HE. Treating women with opioid use disorder during pregnancy in Appalachia: Initial neonatal outcomes following buprenorphine + naloxone exposure. Am J Addict. 2018 Mar;27(2):92-96.

Naloxone is added to deter injection of buprenorphine in abuse/diversion settings.[12] A 2021 systematic review and meta-analysis of five studies (n=258 mother-infant dyads exposed to buprenorphine-naloxone) did not identify serious adverse maternal or neonatal outcomes associated with buprenorphine-naloxone use during pregnancy.[13]

REVIEW

PREGNANCY

Nonclinical Experience

In animal reproduction studies, no embryotoxic or teratogenic effects were observed in mice and rats treated with naloxone hydrochloride during the period of organogenesis at human dose equivalents of 4 and 8 times the human dose.

For full details, the reader is referred to the Pharmacology/Toxicology review by Carlic Huynh PhD.

Review of Pharmacovigilance Database

The applicant searched their pharmacovigilance database for cases relevant to naloxone and pregnancy.[14] No cases were identified.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in PubMed to identify literature regarding the use of naloxone during pregnancy. The reader is referred to the applicant's IR response dated October 1, 2020 for the search strategies that were used. The applicant did not identify new literature not previously described in the Prescribing Information Section 8.1 Pregnancy of the listed drug NARCAN (naloxone hydrochloride; NDA 016636).

DPMH Review of Literature

DPMH previously reviewed the literature for naloxone and noted that naloxone rapidly crosses the placenta and there is potential for fetal and maternal opioid withdrawal. The reader is referred to the previously mentioned 2016 and 2020 DPMH reviews of naloxone for additional details.

DPMH performed an interim search in PubMed, Embase, Micromedex,[15] TERIS,[16] Reprotox,[17] and *Drugs in Pregnancy and Lactation*[18] to find relevant articles related to the use of naloxone during pregnancy. Search terms included "naloxone" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," "miscarriage," and "fetal loss." Literature regarding administration of naloxone to treat a known or suspected

[12] https://www.uptodate.com/contents/overview-of-management-of-opioid-use-disorder-during-pregnancy?search=opioid%20overdose%20pregnancy&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

[13] Link, Heather M. "Buprenorphine-Naloxone Use in Pregnancy: a Subgroup Analysis of Medication to Treat Opioid Use Disorder." *American Journal of Obstetrics & Gynecology MFM* 3, no. 5 (2021):

[14] The applicant's other naloxone products include EVZIO 0.4 mg (NDA 205787) and EVZIO 2 mg (NDA 209862).

[15] https://www.micromedexsolutions.com, accessed 12/20/21.

[16] Truven Health Analytics information. TERIS, accessed 12/20/21.

[17] Truven Health Analytics information. Reprotox, accessed 12/20/21.

[18] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 12th edition. 2022, Philadelphia, PA. online, accessed 12/20/21.

overdose in pregnant patients was not identified. As noted previously, a 2021 meta-analysis of five studies (n=258 mother-infant dyads exposed to buprenorphine-naloxone) did not identify serious adverse maternal or neonatal outcomes associated with buprenorphine-naloxone use during pregnancy.[19] Additional details about the included studies may be found in Appendix A.

Reviewer comment: While the meta-analysis results provide some reassuring human data about naloxone use in pregnancy, there are important limitations due to the differences in dose, route of administration, and length of use between buprenorphine-naloxone and the naloxone auto-injector. Buprenorphine-naloxone is indicated for opioid use disorder and administered orally (buccally or sublingually) for an undetermined period of time. In addition, the dose of the naloxone component is 1-3 mg and minimally absorbed via the oral route.

The American College of Obstetrics & Gynecology[20] noted the following about naloxone and opioid withdrawal in pregnant women: "Although induced withdrawal may possibly contribute to fetal stress, naloxone should be used in pregnant women in the case of maternal overdose in order to save the woman's life."

The American Heart Association's Guidelines 2020 Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) states that management of cardiac arrest in pregnancy should focus on maternal resuscitation and "because of potential interference with maternal resuscitation, fetal monitoring should not be undertaken during cardiac arrest in pregnancy."[21]

MotherToBaby states,

> "There are no studies on whether administration of naloxone for an overdose increases the risk of miscarriage or birth defects…Studies on the combination of buprenorphine/naloxone do not suggest there is an increased risk of low birth weight, prematurity, or stillbirth when taken in the second or third trimester….The effects of opioid withdrawal while pregnant are not well understood."[22]

Reprotox states that based on experimental animal studies, use of naloxone during pregnancy is not expected to increase the risk of congenital anomalies. Reprotox also cited two retrospective studies of combined naloxone and buprenorphine use during pregnancy which did not identify an increased risk of adverse neonatal outcomes.[23,24]

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[19] Link, Heather M. "Buprenorphine-Naloxone Use in Pregnancy: a Subgroup Analysis of Medication to Treat Opioid Use Disorder." *American Journal of Obstetrics & Gynecology MFM* 3, no. 5 (2021):

[20] Committee on Obstetric Practice. Opioid Use and Opioid Use Disorder in Pregnancy. ACOG Number 711. August 2017. Reaffirmed October 2021.

[21] https://cpr heart.org/-/media/cpr-files/cpr-guidelines-files/highlights/hghlghts_2020_ecc_guidelines_english.pdf, accessed 12/22/21.

[22] https://mothertobaby.org/fact-sheets/naloxone/, Naloxone fact sheet last updated July 2, 2020, accessed 12/20/21.

[23] Nguyen L, Lander LR, O'Grady KE, et al. Treating women with opioid use disorder during pregnancy in Appalachia: Initial neonatal outcomes following buprenorphine + naloxone exposure. *Am J Addict*. 2018;27(2):92-96. doi:10.1111/ajad.126876.

[24] Jumah NA, Edwards C, Balfour-Boehm J, Loewen K, Dooley J, Gerber Finn L, Kelly L. Observational study of the safety of buprenorphine + naloxone in pregnancy in a rural and remote population. BMJ Open. 2016 Oct 31;6(10):e011774.

TERIS states the magnitude of teratogenic risk is "undetermined" based on a "limited" quality and quantity of data. TERIS states, "A small risk cannot be excluded, but a high risk of congenital anomalies in the children of women treated with naloxone during pregnancy is unlikely."

LACTATION

Nonclinical Experience

No animal lactation studies have been performed.

Review of Pharmacovigilance Database

The applicant searched their pharmacovigilance database for cases relevant to naloxone and lactation.[25] No cases were identified.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in PubMed to identify literature regarding the use of naloxone and lactation. The reader is referred to the applicant's IR response dated October 1, 2020, for the search strategies that were used. The applicant did not identify relevant literature.

DPMH Review of Literature

In the October 2020 consult for naloxone, DPMH did not identify literature relevant to lactation. In addition, DPMH noted that it is unlikely that naloxone would accumulate in breastmilk or adversely affect the breastfed infant based on the drug's characteristics (small molecular size, short half-life, poor oral bioavailability).

This Reviewer performed an interim literature search in PubMed, Embase, Micromedex,[26] TERIS,[27] Reprotox,[28] and *Drugs in Pregnancy and Lactation*,[29] *Medications and Mothers' Milk*,[30] and LactMed[31] to find relevant articles related to the use of naloxone during lactation. Search terms included "naloxone" AND "breastfeeding" or "lactation." No relevant articles were identified.

In *Medications and Mothers' Milk,* Dr. Hale states,

> "No breastfeeding studies are available. This product poses minimal risk to infants of women not addicted to opiates. However, even small amounts present in milk could accelerate slight withdrawal symptoms in infants of narcotic-addicted women….When administering this medication to a breastfeeding woman for a narcotic overdose, breastfeeding may need to be withheld due to the amount of narcotic in milk, and potential risk of adverse effects (respiratory depression, sedation)."

[25] The applicant's other naloxone products include EVZIO 0.4 mg (NDA 205787) and EVZIO 2 mg (NDA 209862).
[26] https://www.micromedexsolutions.com, accessed 12/16/21
[27] Truven Health Analytics information. Teris, accessed 12/16/21.
[28] Truven Health Analytics information. Reprotox, accessed 12/16/21.
[29] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 12th edition. 2022, Philadelphia, PA. online, accessed 12/16/21.
[30] https://www.halesmeds.com, accessed 12/16/21.
[31] https://www.ncbi.nlm.nih.gov/books/NBK501922/, accessed 12/16/21.

LactMed states,

> "No information is available on the excretion of naloxone into breastmilk. Because it is not orally bioavailable, it is unlikely to affect the breastfed infant. However, if naloxone is required by the mother for an opiate overdose, she should withhold nursing until the opiate is out of her system."

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Reproduction studies conducted in mice and rats demonstrated no adverse effect of naloxone on fertility.

Carcinogenicity studies have not been conducted. Naloxone was weakly positive in the Ames mutagenicity and in the *in vitro* human lymphocyte chromosome aberration test but was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in the *in vivo* rat bone marrow chromosome aberration study.

For full details, the reader is referred to the Pharmacology/Toxicology review by Carlic Huynh PhD.

Review of Pharmacovigilance Database

The applicant searched their pharmacovigilance database for cases relevant to naloxone and fertility.[32]

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in PubMed to identify literature regarding the use of naloxone and fertility. The reader is referred to the applicant's IR response dated October 1, 2020 for the search strategies that were used. The applicant did not identify any relevant articles.

DPMH Review of Literature

This Reviewer performed an interim search in PubMed, Embase, Reprotox to find relevant articles related to the use of naloxone and effects on fertility. Search terms included "naloxone" AND "fertility," "infertility," "contraception," and "oral contraceptives." No relevant articles were identified.

DISCUSSION AND CONCLUSIONS

Pregnancy

Available data of naloxone use in pregnancy over decades of use are limited to observational studies of pregnant patients taking naloxone-buprenorphine for opioid dependence. A 2021 meta-analysis that included 258 mother-infant dyads exposed to buprenorphine-naloxone did not identify serious adverse maternal or neonatal outcomes. There are important limitations due to the difference in dose, route of administration, and timing of exposure between naloxone-buprenorphine treatment for opioid dependence compared to the naloxone auto-injector

[32] The applicant's other naloxone products include EVZIO 0.4 mg (NDA 205787) and EVZIO 2 mg (NDA 209862).

treatment of an opioid overdose, which is a discrete event. Nonetheless, the data provide some reassurance about the use of naloxone in pregnant patients.

While the applicant proposes including labeling language (b) (4) DPMH thinking has evolved since the 2016 PLLR conversion of EVZIO 2 mg labeling. DPMH has recently not recommended inclusion of such language (b) (4) (b) (4)

Lactation

There is no information regarding the use of naloxone in lactating animals or humans. While naloxone in milk could potentially induce withdrawal symptoms in an opioid-dependent infant, the oral bioavailability of naloxone is low and potential transfer in milk would be limited due to the short half-life of naloxone. Additionally, for infants who are not dependent on opioids, the risk of naloxone-induced withdrawal is not a concern. In all infants, however, the amount of opioid in the mother's plasma would also be a clinical consideration for when to resume breastfeeding, and many opioids have a longer half-life of 6-8 hours compared to naloxone. Since multiple factors may contribute to the decision as to when to resume breastfeeding, case by case decision making is needed. DPMH has previously not recommended (b) (4)

Females and Males of Reproductive Potential

Animal fertility data for naloxone do not demonstrate effects on animal fertility and there is no new information regarding naloxone and fertility. Therefore, subsection 8.3 Females and Males of Reproductive Potential will be omitted.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on January 6, 2022. DPMH recommendations are below and reflect the discussions with DAAP. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Life-sustaining therapy for opioid overdose should not be withheld *(see Clinical Considerations).* There is an absence of data on naloxone administered for known or suspected opioid overdose in pregnant patients. Available data from retrospective cohort studies on oral naloxone use in pregnant women for opioid use disorder have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, no embryotoxic or teratogenic effects were observed in mice and rats administered naloxone during organogenesis at doses equivalent to 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
An opioid overdose is a medical emergency and can be fatal for the pregnant woman and fetus if left untreated. Treatment with TRADENAME for opioid overdose should not be withheld because of potential concerns regarding the effects of TRADENAME on the fetus.

Data
Animal Data
Naloxone HCl was administered during organogenesis to mice and rats at doses 4-times and 8-times, respectively, the dose of 10 mg/day given to a 50 kg human (when based on body surface area or mg/m^2). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone HCl.

8.2 Lactation
Risk Summary
Naloxone is minimally orally available and is unlikely to affect the breastfed infant. There is no information regarding the presence of naloxone in human milk, the effects of naloxone on the breastfed infant or on milk production. Published studies in lactating women have shown that naloxone does not affect prolactin or oxytocin hormone levels.

APPENDIX A –
Studies Included in 2021 Meta-Analysis of Buprenorphine-Naloxone Use During Pregnancy

Study	Study design, location, time	Sample	Study groups (n)	Primary outcomes	Secondary outcomes	Results
Gawronski et al[21]	Retrospective cohort, US academic, 2010–2011	Cohort delivered from single labor and delivery unit	B-N (58) Methadone (92)	NAS treatment (yes vs no)	Duration of NAS treatment, total cumulative dose of treatment medication, and duration	Primary: the B-N group had a significantly lower rate (or frequency) of NAS treatment than the methadone group
Jumah et al[19]	Retrospective cohort, rural Canada, 2013–2015	Cohort received care at the district hospital in Northwestern Ontario	B-N (62) No prenatal opioid exposure (618) Prenatal opioid exposure (illicit opioid use or long-acting agonist medication other than B-N) (159)	Birthweight, preterm delivery, congenital anomalies, stillbirth	Gestational age at delivery Apgar score at 1 and 5 min NAS score NAS treatment (yes vs no) Maternal outcome data (CD rate, LOS, hemorrhage, out of hospital delivery)	Primary: no significant differences in the primary outcomes among the 3 groups Secondary: longer neonatal LOS when comparing B-N with no opioid exposure; no other significant differences among the 3 groups
Nechanska et al,[24] 2018 (Czech Republic)	Retrospective cohort, Czech Republic, 2000–2014	Linked national registry data	B-N (22) Buprenorphine (154) Methadone (158)	Neonatal outcomes	—	No significant differences in neonatal outcomes among the 3 groups in both studies Most B-N patients were switched to buprenorphine alone before delivery
Nechanska et al,[24] 2018 (Norway)	Retrospective cohort, Norway, 2004–2013	Linked national registry data	B-N (33) Buprenorphine (99) Methadone (101)	Neonatal outcomes	—	
Wiegand et al[20]	Retrospective cohort, US academic center, 2011–2013	Cohort delivered from single labor and delivery unit	B-N (31) Methadone (31)	NAS treatment (yes vs no), peak NAS score, total morphine treatment, duration of NAS treatment	Neonatal outcomes Maternal outcome data (mode of delivery, analgesia, weight gain, prenatal care visits, MAT dosage)	The B-N group had a significantly lower rate of NAS treatment, lower peak NAS scores, and a shorter duration of hospitalization than the methadone group
Mullins et al[23]	Retrospective cohort, United States, 2014–2018	Cohort obtained care from a community-based perinatal substance program and from a local delivery unit	B-N (85) Buprenorphine (108)	NAS treatment (yes vs no)	Maternal outcome data (prenatal care, pregnancy comorbidities, mode of delivery, LOS, breastfeeding) Neonatal outcome data (gestational age at delivery, sex, birthweight, length, head circumference, 5-min Apgar score, NICU admission, congenital anomalies)	Similar maternal and neonatal outcomes for neonates exposed to B-N vs buprenorphine monoproducts. No evidence of adverse pregnancy outcomes with B-N

NAS score was determined by a modified Finnegan scale taken by a bedside nurse in Jumah et al[19] and by a 13-item modified Finnegan opioid weaning scale taken by a clinical nurse in Wiegand et al.[20] The study of Nechanska et al was a single study reporting outcomes of 2 separate populations.

B-N, buprenorphine-naloxone combination product; *CD*, cesarean delivery; *LOS*, length of stay; *MAT*, medication-assisted treatment; *NAS*, neonatal abstinence syndrome; *NICU*, neonatal intensive care unit.

Link. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. AJOG MFM 2020.

Source: Table Copied from Publication by Link, Heather M. "Buprenorphine-Naloxone Use in Pregnancy: a Subgroup Analysis of Medication to Treat Opioid Use Disorder." *American Journal of Obstetrics & Gynecology MFM* 3, no. 5 (2021).

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JEAN L LIMPERT
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 22, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215457
Product Name and Strength:	naloxone hydrochloride injection, 10 mg (25 mg/mL) autoinjector
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Kaleo Inc.
FDA Received Date:	August 31, 2021
OSE RCM #:	2021-1731
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for naloxone hydrochloride injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed prescribing information (PI), instructions for use, patient information, container label, outer case labeling, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Kaleo previously marketed Evzio (naloxone hydrochloride) 0.4 mg (NDA 205787), which was approved April 3, 2014, and Evzio (naloxone hydrochloride) autoinjector, 2 mg (NDA 209862) which was approved October 19, 2016. Distribution of Evzio 0.4 mg and Evzio 2 mg ceased in December 2016 and May 2020, respectively, according to the most recent annual reports for each application.[a,b]

NDA 215457 is a 505(b)(2) NDA and the listed drug product is Narcan (naloxone hydrochloride), NDA 016636.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] Annual Report: Reporting Period 04-APR-2020 to 03-APR-2021 Distribution Data for Evzio 0.4 mg (NDA 205787). Richmond (VA): Kaleo, Inc.; 2021 APR 30. Available from: \\CDSESUB1\evsprod\nda205787\0144\m1\us\113-ann-rep\distrib-data.pdf.

[b] Annual Report: Reporting Period 19-OCT-2019 to 18-OCT-2020 Distribution Data for Evzio 2 mg (NDA 209862). Richmond (VA): Kaleo, Inc.; 2020 DEC 17. Available from: \\CDSESUB1\evsprod\nda209862\0291\m1\us\113-ann-rep\distrib-data.pdf.

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed Naloxone hydrochloride patient information did not identify areas of vulnerability that may lead to medication errors. However, the proposed prescribing information, container label, outer case labeling, carton labeling, and instructions for use may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Kaleo Inc. Note that DMEPA 1 is evaluating the Human Factors validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMEDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The first bullet point, (b) (4) could cause confusion if it was misinterpreted to mean (b) (4)	Misinterpretation of the wording (b) (4) .	Reword the statement (b) (4) to express the connotation that the naloxone auto-injector should be administered as soon as possible after recognizing a situation requiring its administration. For example, "Administer Naloxone Auto-injector 10 mg as soon as possible after known or suspected opioid exposure or overdose because prolonged respiratory depression…"
2.	The fourth bullet point reads "Periodically visually inspect NALOXON (b) (4) through	From a medication error perspective, this statement could result in the administration of contaminated or	We defer to the expertise of the review team to evaluate this statement from a risk *versus* benefit perspective.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the viewing window for particulate matter. Request a replacement if the solution is cloudy or contains particles, or if the glass container is damaged. (b) (4) [redacted] ”	deteriorated drug product. It is unclear if the benefit of using the naloxone autoinjector when the solution is cloudy or contains particles, or if the glass container is damaged, outweighs the risks that may be associated with the contaminated product.	

5 RECOMMENDATIONS FOR KALEO INC.

Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors validation study results.

Table 3. Identified Issues and Recommendations for Kaleo Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	As currently presented, the format of the expiration date is denoted as, “EXP: MM/YYYY” and it is unclear if the month portion, “MM,” of the expiration date format will use alphabetical or numerical characters.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug errors. For example, confusion has occurred with use of the alphabetical abbreviation “JU,” which can represent both “June” and “July” and the alphabetical abbreviation “MA,” which can represent both “March” and “May.”	Clarify if you intend to use only numerical characters to express each portion of the expiration date.
Outer Case Labeling			

Table 3. Identified Issues and Recommendations for Kaleo Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, the storage statement on the outer case labeling reads (b) (4) We note there is no additional storage information on the container label.	(b) (4)	Revise (b) (4) to "Store below 25°C (77°F), excursions permitted up to 40°C (104°F). Do not freeze."
General Comment (Container Label and Carton Labeling)			
1.	The "each 0.4 mL" statement may be improved to better clarify the dose amount and dose volume delivered by the autoinjector. For example, consider revising to state, "This autoinjector delivers one 10 mg dose of naloxone in 0.4 mL. Each 0.4 mL also contains 3.34 mg sodium chloride and water for injection."		
Instructions for Use			
1.	Page 2, Step 1 contains a typo, "if (b) (4) (b) (4) is frozen, do no wait for it to thaw," which may lead to confusion.	Correcting the typo will help alleviate confusion.	Correct the statement to, "if (b) (4) is frozen, do not wait for it to thaw."

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for naloxone hydrochloride that Kaleo Inc. submitted on August 31, 2021, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and naloxone hydrochloride		
Product Name	Narcan (RLD)	Naloxone hydrochloride (proposed)
Initial Approval Date	April 13, 1971	n/a
Active Ingredient	Naloxone hydrochloride	
Indication	1. Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics; nalbuphine, pentazocine, butorphanol, and cyclazocine. 2. Diagnosis of suspected or known acute opioid overdosage.	(b) (4)
Route of Administration	Intravenously, intramuscularly, subcutaneously	Intramuscular or subcutaneous
Dosage Form	Solution for injection	
Strength	0.02 mg/mL, 0.4 mg/mL, 1 mg/mL	10 mg/0.4 mL
Dose and Frequency	May be diluted (2 mg naloxone in 500 mL of normal saline or	Administer 10 mg as quickly as possible

	5% dextrose). Opioid Overdose – known or suspected: initial dose of 0.4 to 2 mg, repeated at 2-to-3-minute intervals. If no response after 10 mg has been administered, question diagnosis of opioid toxicity. Postoperative Opioid Depression: for partial reversal during surgery, smaller doses are usually sufficient. Initial reversal of respiratory depression, inject in increments of 0.1 to 0.2 mg at 2- to 3-minute intervals to desired degree of reversal	
How Supplied	0.4 mg/mL: 10 mL multiple dose vial (box of 1) 1 mg/mL: 10 mL multiple dose vial (box of 1) 0.02 mg/mL: 2 mL unit dose ampule (box of 10) 0.4 mg/mL: 1 mL unit dose ampule (box of 10) 1 mg/mL: 2 mL unit dose ampule (box of 10)	Package containing 10 autoinjectors (AI), each designed to deliver one 10 mg injection
Storage	Store at 25 °C (77°F); excursions permitted to 15 to -30 °C (59 to -86 °F). Protect from light and store in carton until contents have been used.	(b) (4) [redacted]

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 30, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms "naloxone hydrochloride" and limited our search results to naloxone injection products only. Our search identified 11 previous reviews[c,d,e,f,g,h,i,j,k,l,m], and we considered our previous recommendations to see if they are applicable for this current review. We determined that the previous recommendations are not applicable to this application.

[c] Borders-Hemphill. Label and Labeling Review for naloxone hydrochloride (NDA 205787). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 DEC 11. RCM No.: 2013-1727.

[d] Shah, M. Human Factors Study Results Review Memo for Evzio (NDA 205787). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 25. RCM No.: 2015-1538.

[e] Shah, M. Postmarket Medication Error Review for Evzio (NDA 205787). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 DEC 28. RCM No.: 2015-2427.

[f] Calderon, M. Label and Labeling Review for Evzio (NDA 205787/S(b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 SEP 22. RCM No.: 2016-940.

[g] Schlick, J. Postmarket Medication Error Review for Evzio (NDA 209862). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 12. RCM No.: 2017-2439.

[h] Shah, M. Human Factors and Label and Labeling Review for Evzio (NDA 209862/S(b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 07. RCM No.: 2018-2805.

[i] Flint, J. URRA and CA and Label and Labeling Review for Zimhi (NDA 212854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 24. RCM No.: 2019-8 and 2019-15.

[j] Flint, J. URRA Label and Labeling Review for Narcan (NDA (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 25. RCM No.: 2019-2036 and 2019-2037.

[k] Johnson, C. Label and Labeling Review for Zimhi (NDA 212854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 04. RCM No.: 2019-8-1.

[l] Johnson, C. Label and Labeling Review for Zimhi (NDA 212854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 AUG 26. RCM No.: 2019-8-2.

[m] Clark, C. Label and Labeling Review Memorandum for Zimhi (NDA 212854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEP 29. RCM No.: 2019-8-3.

APPENDIX C. - N/A

APPENDIX D. - N/A

APPENDIX E. - N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[n] along with postmarket medication error data, we reviewed the following Naloxone hydrochloride labels and labeling submitted by Kaleo Inc.

- Container labeling received on August 31, 2021
- Outer Case labeling received on August 31, 2021
- Carton labeling received on August 31, 2021
- Instructions for Use (Image not shown) received on August 31, 2021, available from \\CDSESUB1\evsprod\nda215457\0001\m1\us\114-label\1141-draft-label\ifu-pat-info-ij5060-00.pdf
- Medication Guide (Image not shown) received on August 31, 2021, available from \\CDSESUB1\evsprod\nda215457\0001\m1\us\114-label\1141-draft-label\patient-info-ij5060-00-pdf.pdf
- Prescribing Information (Image not shown) received on August 31, 2021, available from \\CDSESUB1\evsprod\nda215457\0001\m1\us\114-label\1141-draft-label\pi-ij5070-00-pdf.pdf

[n] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

F.2 Label and Labeling Images

Carton Labeling

(b) (4)

Outer Case Labeling

Container Label

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAMON A BIRKEMEIER
11/22/2021 12:00:49 PM

VALERIE S VAUGHAN
11/22/2021 12:21:19 PM