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RESEARCH**

APPLICATION NUMBER:

205787Orig1s000

OTHER REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: September 30, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

TO: Diana Walker, Regulator Project Manager, CDER/OND/ODEII/DAAAP

SUBJECT: NDA 205787
Applicant: Intelliject
Drug: Naloxone
Device: autoinjector
Intended Use: treatment of opioid overdose
CTS Tracking (b) (4)

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

Overview and Recommendation

The Division of Anesthesia, Analgesia, and Addiction Products, Office of New Drugs, Center for Drug Evaluation and Research requested a human factors consultative review of Naloxone Auto-Injector (NAI) Human Factors Program Report contained in NDA 205787 submitted by Intelliject. The device is an autoinjector for emergency treatment of opioid overdose.

Intelliject conducted several preliminary analyses and six formative studies. Results from these analyses were used to optimize labeling, instructions for use and device design user interface such as safety guard arrow design, and electronic voice prompt system. Intelliject also conducted a human factors validation study with forty participants (19 juveniles and 21 adults). The participants performed a simulated injection with NAI without training. Of the 40 participants, four participants failed to deliver an effective dose. Root cause analysis, and review of post-test user interviews indicated that the device was not firmly pressed against the skin to engage the injection mechanism, the device as not hold at the injection site for a full second, and a trainer device was used instead of the study device.

Based on post-test interview responses, Intelliject considered changes (b) (4). However, Intelliject believes that if a user commits a critical use error, the residual risk is that the patient would be receiving the current standard of care from paramedic and EMT personnel. Regarding the issue of holding the device at the injection site for one second, Intelliject confirmed that the injection time of the needle and dispensing time of the drug is less than (b) (4) seconds. In addition, the voice prompt provides a device count down “five, four, three, two, one” after the injection is initiated and indicates that injection is complete. Regarding the use of a trainer device, Intelliject expects that user would immediately recognize that it is a trainer device because the voice prompts states that it is a trainer device.

The consultant reviewed and discussed Intelliject’s study analyses and residual risks evaluation of observed use errors and difficulties with team lead. We believe that the Sponsor has conducted adequate human factors study and provided adequate rationale and justification for the residual risks. The consultant also believes having this device available for use prior to emergency responder arriving to the scene can provide value-added to opioid overdose management in that it can provide early and prompt response to the patient. The reviewer does not have any outstanding concerns with regards to the device user interface, or the human factors validation study report.

Appendix 1: Summary of Human Factors Related Information

Intelliject provided the following information their human factors program report:

1. Summary of use-related risks and proposed mitigation
2. Summary of formative usability evaluation results
3. Complete summative design validation study report

The following table provides a summary of potential use errors and associated levels of severity i.e. critical, moderate, and minor.

Severity	Potential Use Errors
CRITICAL Error could lead to patient <u>not receiving a dose of naloxone HCl</u>	○ User assumes drug is satisfactory when drug has expired or degraded
	○ User tries to use a previously-used device
	○ User does not pull off Red Safety Guard
	○ User pulls device away from outer thigh (or muscle) prematurely after activation (User does not hold in place at least ^(b) ₍₄₎ seconds; actual injection occur in less than ^(b) ₍₄₎ seconds)
	○ User decides not to inject the dose
	○ User places device in wrong location (other than outer thigh or appropriate muscle)
	○ User does not place base on thigh (or an alternative appropriate location). Puts hand over wrong end; unintentional self-injection
	○ User pushes base with finger or against some other site other than injection site; premature activation
○ User confuses NAI with NAI Trainer and uses NAI Trainer on patient	
MODERATE Error could lead to an <u>ineffective dose or significant delay in receiving a dose of naloxone HCl</u>	○ User moves device while trying to inject leading to increased potential for ineffective dose
	○ User misplaces devices for future use
	○ User has difficulty determining how to pull safety guard off
	○ User does not apply sufficient force to activate injection
	○ User has difficulty pulling device out of outer case with sufficient force
	○ User attempts to disassemble the device causing potential for premature activation; could lead to unintentional self-injection into hand, arm or other body part
○ User drops the device after safety guard is removed; premature activation	
MINOR Error causes <u>user frustration or slight delay in receiving a dose of naloxone HCl</u>	○ User could misplace instructions or NAI Trainer for future use; forgetting key steps
	○ User drops device before or while removing outer case
	○ User has difficulty pulling device(s) out of packaging
	○ User does not hold in place for full 5 seconds (but at least greater than ^(b) ₍₄₎ seconds)
	○ User does not understand how to open package or how to open the package
	○ User ignores instruction leaflets and uses device; lack of training
	○ User ignores audible instructions missing steps
	○ User ignores use of instructions on device
○ User removes safety guard prematurely and tries to replace safety guard	

The following tasks are identified as critical tasks for the NAI and will be included in the validation study:

1. Select NAI from packaging (versus NAI Trainer)
2. Remove NAI from its outer case
3. Pull off red safety guard
4. Place black end against the patient's outer thigh
5. Push NAI firmly against the patient's outer thigh
6. Hold NAI in place for at least one second

Intelliject conducted several preliminary analyses and six formative studies. Results from these analyses were used to optimize labeling, instructions for use and device design user interface such as safety guard arrow design, and electronic voice prompt system.

Intelliject also conducted a human factors validation study with forty participants (19 juveniles and 21 adults). The participants performed a simulated injection with NAI without training. Of the 40 participants, four participants failed to deliver an effective dose. Root cause analysis, and review of post-test user interviews indicated that the device was not firmly pressed against the skin to engage the injection mechanism, the device as not hold at the injection site for a full second, and a trainer device was used instead of the study device.

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

- Five juvenile participants used the trainer instead of study device but post-test user interview showed that these participants confirmed that they knew which device was which, and stated that they used the trainer intentionally because the simulation as a test or pretend situation.
- Four juvenile participants experienced difficulty with pulling off red safety guard. Intelliject confirmed that all adult participants could remove the red safety guard, and four juvenile participants experienced some difficulty initially but were able to pull it off.
- Four adult participants and two juvenile participants did not inject into the outer thigh but instead, they injected into the front or back of the thigh, inner thigh, etc. Intelliject confirmed that NAI is indicated for subcutaneous or intramuscular administration. While Intelliject has determined that the outer thigh is the ideal injection site location, if NAI were to be administered into the thigh, legs or upper arms/shoulder, they stated that the patient would still receive a SC or IM injection.
- Two participants (one adult and one juvenile) did not press device firmly against the skin for device activation. Based on post-test interview responses, Intelliject considered changes to (b) (4)
However, Intelliject believes that if a user commits a critical use error, the residual risk is that the patient would be receiving the current standard of care from paramedic and EMT personnel.
- Two juvenile participants did not hold the device in place for at least 1 second. Intelliject confirmed that the injection time of the needle and dispensing time of the drug is less than (b) (4) seconds. In addition, the voice prompt provides a device count down “five, four, three, two, one” after the injection is initiated.

Based on these analyses, the consultant finds the human factors study acceptable, and no further optimization on the design and/or labeling is necessary.

Appendix 2: Device Information

NAI is a compact drug delivery system intended for immediate administration of a prescribed dose of naloxone HCl (0.4 mg) in patients suffering from respiratory depression due to an opioid overdose. The device is a (b) (4), needle-based system that allows a user to deliver the prescribed dose of naloxone HCl into a patient once activated. The needle is fully retracted within the device housing following use. NAI also includes an enhanced labeling feature in the form of an electronic audible and visual prompt system that assists in guiding a user through the injection process (through the use of voice prompts, beeps and LEDs). This electronic prompt system works independently from the mechanical functionality of the naloxone delivery system in the device. Overall dimensions of NAI (height, width, thickness) are 3.4" x 2.0" x 0.64" with an approximate weight of 64 grams.



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/s/

DIANA L WALKER

04/02/2014

This CDRH review was entered for
QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

505(b)(2) ASSESSMENT

Application Information		
NDA # 205787	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Evzio Established/Proper Name: naloxone hydrochloride injection USP Dosage Form: autoinjector Strengths: 0.4 mg (0.4 mg/0.4 mL)		
Applicant: kaleo, Inc.		
Date of Receipt: December 20, 2013		
PDUFA Goal Date: June 20, 2014		Action Goal Date (if different): April 2, 2014
RPM: Diana Walker		
Proposed Indication(s): EVZIO is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, and is intended for immediate administration as emergency therapy in settings where opioids may be present.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<i>published literature</i>	<i>Nonclinical pharmacology, pharmacokinetics, and toxicology. Also human clinical pharmacology, safety and efficacy.</i>
<i>NDA 016636: Narcan (naloxone hydrochloride)</i>	<i>FDA's previous finding of safety and effectiveness (clinical and nonclinical)</i>

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Kaleo Inc submitted a 505(b)(2) NDA 205787 for EVZIO NAI and proposed to rely on the Agency’s previous finding of the safety and efficacy of the listed drug, Narcan (NDA 016636). Because Narcan has been discontinued and is no longer marketed and generic naloxone HCl products are commercially available in pre-filled syringes and vial presentations, in the pivotal comparative bioavailability Study IJ-900DV-03O, the Applicant used the generic product to Narcan, International Medicinal System (IMS) Limited’s 2 mg/2 mL single dose disposable LUER-JET naloxone HCl injection USP pre-filled syringe (National Drug Code number: 0548-1469-00, ANDA #072076) to establish the PK bridge. The study was titled: *Study IJ-900DV-03O, a randomized, single-dose, single-blind, two sequence, two-period crossover bioavailability, safety and tolerability study in healthy human volunteers.*

No new nonclinical toxicology studies were submitted in this NDA, but the Applicant conducted a literature review to determine if there were new data published since the time of approval of the referenced NDA that impacted the safe use of drug product. These articles were reviewed from a nonclinical perspective to determine if they contained adequate data to further inform product labeling and safety.

The Applicant also performed an analysis of the literature to support the safety of Evzio from a clinical perspective, and literature supporting safety in the pediatric population. The Applicant submitted an analysis of a PubMed database search for published data relevant to the safety and efficacy of naloxone. The analysis of the literature supports the safety and effectiveness of naloxone for the treatment of respiratory depression secondary to opioid overdose.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
If "NO," proceed to question #5.
If "YES", list the listed drug(s) identified by name and answer question #4(c).
Narcan (naloxone hydrochloride)

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO
If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
<i>Narcan (naloxone hydrochloride)</i>	<i>NDA 016636</i>	<i>Y</i>

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Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
 N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

- d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

NDA 016636: Narcan (naloxone hydrochloride)

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a change in dosage form, from injection to pre-filled autoinjector and this application is a new combination (Type 3/Type 4 new NDA).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer “N/A”
If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are

listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): **Yes, there are approved generics such as ANDA 072076. But they are not the same dosage form (autoinjector).**

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

DIANA L WALKER
04/02/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: NDA 205787/EVZIO (naloxone hydrochloride injection USP)

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

PMR Schedule Milestones:

Final Protocol Submission:	<u>08//29/2014</u>
Study/Trial Completion:	<u>09/31/2014</u>
Final Report Submission:	<u>10/29/2014</u>
Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This study is appropriate for a PMR (to conduct a study to demonstrate that the needle length is safe for use in patients less than one year of age during expected conditions of use) because this autoinjector device has been marketed filled with other drug products, and there have been no previous reports of needle breakage. Further, the patient population most at risk is young children, theoretically the neonatal age group, given their relatively small amount of subcutaneous tissue compared to older age groups. A scenario of opioid overdose in this age group is expected to be very infrequent. Therefore, the use of this product in small children would be very rare and the striking of bone has not been seen during development, and remains a theoretical concern. Most importantly, the benefit of saving a child who has had an overdose from potential death outweighs the very small risk of the needle striking bone.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The PMR is a study to assess the likelihood of needle breakage, and poses no risk to actual subjects.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
In vitro study described under question 4
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
In vitro study described under question 4
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

DIANA L WALKER
04/01/2014

JUDITH A RACOOSIN
04/01/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: April 1, 2014

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From: M. Isabel Tejero, Acting Lead, QSWG/DMQ/OC/CDRH/OMPT.
WO-66, Room 3554

Applicant: Kaléo Pharma Inc. (formerly Intelliject)
111 Virginia St, Suite 300
Richmond, VA 23229
FEI # 3007135538

Application # NDA 205787 (IND 112292)

Product Name: Evzio, a Naloxone Auto-Injector (NIA), containing 0.4 mg of
naloxone hydrochloride injection, USP

Consult Evaluation of NDA 205787 for approvability based on the results
Instructions: of the inspection of (b) (4).

The Office of Compliance at CDRH received a consult request from CDER to evaluate the results of the inspection conducted at (b) (4), located at (b) (4), and with FEI # (b) (4), and provide final approvability recommendation for NDA 205787.

This is a rolling review on a high priority clock (6 months). Due to the impact on the Public Health, the approval of the application has been given the highest priority by CDER.

(b) (4)

This is a single dose injector (figure 1) with a dosage of 0.4 mg (0.4 mg/0.4 mL) naloxone hydrochloride injection, USP.

(b) (4)



Figure 1
(b) (4)



Evaluation of Inspection findings at (b) (4)

An inspection was conducted at (b) (4), located at (b) (4), and with FEI # (b) (4), from (b) (4). The district issued a three observation form FDA-483 at the conclusion of the inspection. The observations and additional findings during the inspection were discussed during a phone call conducted on (b) (4), which included CDRH Compliance, one of the investigators, and officers from NEW-DO compliance, OCP, and CDER's Compliance.

The inspection covered the assembly and packaging of the Evzio autoinjector. Additionally, CAPA and purchasing controls were evaluated.

The following three observations were written on the form FDA-483:

1. OBSERVATION 1: A process whose results cannot be fully verified by subsequent inspection and test has not been adequately validated according to established procedures.

(b) (4)

Evaluation: The firm is currently waiting for the approval of the final labeling by CDER before the complete the process validation of the commercial manufacturing line. (b) (4)

(b) (4)

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

A. (b) (4)

B. (b) (4)

(b) (4)

3. OBSERVATION 3: Procedures for corrective and preventive action have not been

adequately established. Specifically,

(b) (4)

There were no additional findings pertaining to the Medical Device Regulation to be discussed. The investigators did not find any additional issues.

CDRH Office of Compliance Inspection Classification Recommendation

Based on the nature of the observations in form FDA-483, and the conversations with the investigators, NWE-DO and CDER compliance, the Office of Compliance at CDRH recommends that the inspection conducted from (b) (4) at (b) (4), located in (b) (4), and with FEI # (b) (4), is classified VAI (Voluntary Action Indicated).

CDRH Office of Compliance NDA Approvability Recommendation

The Office of Compliance at CDRH has completed the evaluation of application NDA 205787, including the firm's response to the deficiency letter dated January 22, 2014, and the form FDA-483 issued at the end of the inspection of the (b) (4).

The Office of Compliance recommends that NDA 205787 is approved based on the following facts:

- A fully satisfactory desk review of application NDA 205787, as it pertained to Medical Device filing regulatory requirements.
- Adequate inspectional history of (b) (4).
- A VAI classification recommendation by CDRH/OC of the inspection of (b) (4) (FEI # (b) (4)) after thorough discussions with the New England District's investigators and compliance officer.

M. Isabel Tejero del Rio, MD, Ph.D.

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

/s/

DIANA L WALKER

04/01/2014

Entered into DARRTS for CDRH reviewer:
M. Isabel Tejero del Rio, MD, Ph.D.,
Acting Lead, QSWG/DMQ/OC/CDRH/OMPT



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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Pediatric and Maternal Health Staff – Maternal Health Review

Date: March 28, 2014

From: Carol H. Kasten, MD, Medical Officer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa S. Tassinari, Ph.D. DABT, Senior Clinical Advisor,
Pediatric and Maternal Health Staff, Maternal Health Team

Lynne P. Yao, MD, OND IO Associate Director
Pediatric and Maternal Health Staff

To: Division of Anesthesia, Analgesia, and Addiction Products
(DAAAP)

NDA: NDA 205787

Drug: Evzio® (Naloxone Auto-Injector)

Subject: PLR labeling conversion

Sponsor: Kaleo (formerly Intelliject, Inc)

Consult Request: “Please make sure the labeling is consistent with the upcoming pregnancy labeling rule.”

INTRODUCTION

Evzio (naloxone hydrochloride), NDA 205787, was submitted on December 20, 2013. It was granted a Fast-Track designation under IND 112292 on January 15, 2013. Naloxone hydrochloride will be delivered using a new autoinjector, however, the active ingredient has been approved since 1971 and several generic naloxone products are available. The applicant is seeking approval for the following indications:

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

DAAAP consulted the Pediatric and Maternal Health Staff, Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the Evzio labeling. This review provides suggested revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Regulatory History

The Pre-IND meeting for this drug product was held August 16, 2011. At the meeting the Division determined that a 505(b)(2) path would be acceptable and discussed several issues including those related to product quality and the design of the autoinjector (see meeting minutes dated September 1, 2011 in DARRTS).

At the Pre-NDA meeting held June 4, 2013, the applicant stated plans to file a 505(b)(2) application with the Reference Listed Drug (RLD) product Narcan® (NDA 016636) and naloxone hydrochloride (ANDA 072076) to establish efficacy through bioavailability studies with the RLD.

NARCAN® (naloxone hydrochloride) was approved in multiple strengths (0.02 mg/mL, 0.4 mg/mL, and 1 mg/mL) for use as an opioid antagonist. Narcan's last labeling update was in 2003. Narcan carries a Pregnancy Category C. Narcan was withdrawn from the market in 2010 but Narcan was not withdrawn from sale for reasons of safety or efficacy. There are currently six generic naloxone drug products marketed, under ANDAs 070172, 070254, 070256, 070639, 072076 and 204997. Five of the six ANDAs have a Pregnancy Category C. One, ANDA 070639, carries a Pregnancy Category B.

Reviewer comment: The reviewer notes that there are differences in Pregnancy Category listing between Narcan and some of the generic products. This is discussed in more detail below.

Naloxone hydrochloride

Naloxone is a competitive opioid antagonist which interacts with all opioid receptors. Its highest affinity is for the μ opioid receptor.^{1,2} Naloxone is administered parenterally as it is almost completely metabolized by the liver if given orally.¹ Naloxone is devoid of any agonist effect and is relatively lipid soluble with excellent CNS bioavailability.² Small doses of naloxone (0.4-0.8 mg) given intramuscularly or intravenously rapidly reverse the effects of exogenous opioids. Doses up to 5 to 10 mg of naloxone may be required to reverse the effect of potent opioids.² The $t_{1/2}$ of naloxone is about 1 hour;^{1,2} however, its clinically effective duration may be even less.¹

The applicant proposes to deliver naloxone (0.4 mg), IM or SQ, via a user-actuated, single-use, auto-injector which provides audible instructions for use and visual cues to guide the non-medically trained user. The routes of administration proposed for this NDA have been previously approved.

DISCUSSION

Pregnancy and Lactation Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount.

Pregnancy Category

As noted above, there is a labeling discrepancy in Pregnancy Category between ANDA 70639, a Category B drug, and the other five currently available ANDAs and the RLD

¹ Yaksh TL, Wallace MS, Chapter 18. Opioids, Analgesia, and Pain Management. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e*. New York: McGraw-Hill; 2011.

<http://accessmedicine.mhmedical.com/content.aspx?bookid=374&Sectionid=41266224> . Accessed March 15, 2014.

² Olson KR. Chapter 38. Poisoning. In: Papadakis MA, McPhee SJ, Rabow MW. eds. *CURRENT Medical Diagnosis & Treatment 2014*. New York: McGraw-Hill; 2014.

<http://accessmedicine.mhmedical.com/content.aspx?bookid=330&Sectionid=44291041> Accessed March 15, 2014.

Narcan which are all Category C. Products in Category C require that animal reproduction studies demonstrate an adverse effect on the fetus in the absence of well-controlled studies in pregnant women whereas Category B products have not been shown to pose a risk to the fetus in animals. The REPROTOX® database indicates that use of naloxone during pregnancy is not expected to increase the risk of congenital anomalies.³ It cites studies in which mice and hamsters were given naloxone during pregnancy. No teratogenicity was observed even with doses of naloxone 2500 to 20,000 times (in mice) and 9200 to 98,000 times (in hamsters) the dose used for single injections in humans. REPROTOX® does report there were some behavioral changes from prenatal naloxone exposure in rats;⁴ however, these changes in rats did not occur in a dose-dependent manner and only some of them persisted into adulthood.⁴

PMHS Maternal Health Team discussed the Evzio Pregnancy Category rating with Pharmacology-Toxicology. Their review of the naloxone animal data is that it is consistent with a Category B, which they recommend for Evzio. This reviewer agrees with the recommendation from Pharmacology-Toxicology. There are no animal studies demonstrating that naloxone has an adverse effect on the fetus.

Transplacental Transfer of Naloxone

Numerous studies in pregnant women as well as research in animals have reported that naloxone administered to the mother rapidly crosses the placenta to the fetus. An *in vitro* human placental perfusion study has demonstrated naloxone rapidly crosses the placenta in as little as 2 minutes after maternal administration.^{5,6} In a placebo controlled study of 54 non-opioid dependent pregnant women near term, the women were administered 0.4 mg of naloxone.⁷ In the first hour following administration, increased gross fetal body and breathing movements were significantly increased consistent with rapid transplacental transfer of the drug.⁷ The authors commented that their data suggest endogenous endorphins may be involved in modulation of fetal behavior.⁷

Reviewer comments:

Evzio labeling contains no information on trans-placental passage of naloxone, although this is well established^{6,8} and was included in the 2003 labeling for Narcan. Nor does it comment on possible induction of fetal distress in an opioid-dependent pregnant woman

³ Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed March 6, 2014.

⁴ Shepanek NA, Smith RF, Tyer ZE, et al.: Behavioral and neuroanatomical sequelae of prenatal naloxone administration in the rat. *Neurotoxicol Teratol* 11:441-446, 1989.

⁵ Kopecky EA, Simone C, Knie B, Koren G: Transfer of morphine across the human placenta and its interaction with naloxone. *Life Sci* 1999;65:2359-71.

⁶ Hibbard BM, Rosen M, Davies D. Placental transfer of naloxone. *Br J Anaesth*. 1986 Jan;58(1):45-8.

⁷ Arduini D, Rizzo G, Dell'Acqua S et al. Effect of naloxone on fetal behavior near term. *Am J Obstet Gynecol* 1987 Feb;156:474-8.

⁸ Jurand A: The interference of naloxone hydrochloride in the teratogenic activity of opiates. *Teratology* 31:235-240, 1985.

although this has been reported in women^{9,10} and animal models^{4,11,12} and was also included in the 2003 Narcan labeling. PMHS recommends that this information be included in Evzio labeling.

Lactation

A review of Hale's Medications and Mother's Milk¹³ reveals that naloxone is poorly absorbed orally. The Drugs and Lactation Database (LactMed)¹⁴ states no information is available on the presence of naloxone in breastmilk and concurs with Hale's that it is not orally bioavailable.¹⁵

CONCLUSIONS

The pregnancy subsection of Evzio labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The Nursing Mothers subsection of the Evzio labeling was revised to comply with current labeling recommendations.

Pregnancy Category

The choice of Pregnancy Category B is recommended by Pharmacology-Toxicology and PMHS-MHT agrees.

RECOMMENDATIONS

PMHS participated in labeling meetings with the Division. Final labeling is subject to negotiations with the applicant and may not fully reflect changes suggested here. See the final approved labeling in DARRTS, which is appended to the approval letter. The following are the PMHS-MHT's recommendations for Evzio Pregnancy and Nursing Mothers labeling.

⁹ Hill RM, Desmond MM. Management of the narcotic withdrawal syndrome in the neonate. *Pediatr Clin North Am* 1963 Feb;10:67-86.

¹⁰ Zuspan FP, Gumpel JA, Mejia-Zelaya A et al. Fetal stress from methadone withdrawal. *Am J Obstet Gynecol*. 1975 May 1;122(1):43-6.

¹¹ Jones KL, Barr GA. Opiate Withdrawal in the Fetal Rat: A Behavioral Profile. *Pharmacol Biochem Behav* 2000;66:419-424.

¹² Umans JG, Szeto HH: Precipitated opiate abstinence in utero. *Am J Obstet Gynecol* 151:441-4,1985.

¹³ Hale's 2012 Medications and Mother's Milk. 15th Edition, Amarillo, TX.

¹⁴ The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed provides information, when available, on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹⁵ U.S. National Library of Medicine. National Institutes of Health. LactMed: A New NLM Database on Drugs and Lactation. (2013). Retrieved March 6, 2014 from <http://toxnet.nlm.nih.gov/cgi-bin/sis/search>.

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well-controlled studies with Evzio in pregnant women. Animal studies were conducted with naloxone hydrochloride given during organogenesis in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day. These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride. Because animal reproduction studies are not always predictive of human response, naloxone hydrochloride should be used during pregnancy only if clearly needed.

Clinical Considerations

Naloxone crosses the placenta, and may precipitate withdrawal in the fetus as well as in the opioid-dependent mother. The fetus should be evaluated for signs of distress after Evzio is used. Careful monitoring is needed until the fetus and mother are stabilized.

Data

Animal Data

Naloxone 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 hydrochloride.

8.3 Nursing Mothers

It is not known whether naloxone is present in human milk. Because many drugs are present in human milk, exercise caution when naloxone is administered to a nursing woman.

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/s/

CAROL H KASTEN
03/28/2014

LYNNE P YAO
03/30/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

From: Erica L. Wynn, MD, MPH Medical Officer
Pediatric and Maternal Health Staff (PMHS)

Through: Hari Cheryl Sachs, MD, Team Leader
Lynne Yao, MD, OND Associate Director,
Pediatric and Maternal Health Staff (PMHS)

To: Division of Anesthesia, Analgesia, and Addiction
Products

NDA: 205787
Drug: Naloxone Auto-Injector (NAI)

Sponsor: Kaleo, Inc. (Formerly Intelliject)

Approved indications: None

Proposed indications:  (b) (4)

Consult Question: Assist in developing language for Section 8.4 of the PLR labeling for this product. Assure that the language is consistent with required pediatric information in the labeling guidance and regulations.

Materials Reviewed

- PMHS consult request dated March 4, 2014, (DARRTS Reference ID: 3464241)
- Sponsor’s submission dated March 10, 2014
- Annotated draft labeling accessed from the original submission dated August 23, 2013.
- Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling dated February 2013.

Introduction, Background, and Relevant Regulatory History:

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) is currently evaluating several auto-injector products that will deliver naloxone hydrochloride in the outpatient community setting. Naloxone is a narcotic antagonist that prevents or reverses the effects of opioids including respiratory depression, sedation, and hypotension. The exact mechanism of action of naloxone is not fully understood.

In May of 2013, DAAAP consulted PMHS in preparation for a Pre-NDA meeting for a new drug-device single-use autoinjector for naloxone (IND 112292). (Refer to PMHS consult review for IND 112292, DARRTS Reference ID 3322614, dated June 19, 2013.) Specifically PMHS was asked to provide comment on the following question, “Does the FDA agree that NAI (naloxone auto-injector) does not represent a new dosing regimen of naloxone in the pediatric population, and is, therefore, not subject to PREA?” PMHS noted that the sponsor proposed a dose of 0.4 mg of naloxone be administered intramuscularly or subcutaneously in patients weighing 4 kg (9 pounds) or greater. Because the current prescribing information for Narcan (naloxone hydrochloride injection), the referenced drug, provides flexible dosing based on weight for pediatric patients (as opposed to fixed dosing), PMHS concluded the product triggered PREA as a new dosing regimen. Furthermore, the proposed NAI (naloxone auto-injector) product was subject to PREA because of the new proposed indication, which included “(b) (4) of respiratory depression caused by natural and synthetic opioids....” The (b) (4) population was considered to be a new patient population not currently in the approved labeling.

Studies conducted under IND 112292 were subsequently used by Kaleo, Inc., to support NDA 205787 for Naloxone Auto-Injector (NAI) submitted December 20, 2013. In the NDA application, (b) (4)

[Redacted]

(b) (4)

In February 2014, after the submission of NDA 205787, DAAAP again consulted PMHS with questions regarding the appropriateness of requiring an age-appropriate formulation that would allow for weight-based dosing in the outpatient clinical setting. The Division believed that the relevant formulation for all pediatric patients would be the fixed-dose adult dose in the proposed product. DAAAP also asked if PK and safety studies using the full adult dose were sufficient to satisfy the PREA requirements for naloxone products intended to be used in the community. (Refer to DARRTS document 3461575, PMHS review dated February 27, 2014 under IND 112292) PMHS advised DAAAP that the applicant would not likely qualify for a full waiver, however existing data available in the literature and from previous studies with the referenced drug could potentially be leveraged to support the safety and efficacy of the proposed fixed doses for the entire pediatric age range. In addition, PK and safety studies may be sufficient to support labeling and to fulfill the PREA requirement once a dose was chosen. Finally, PMHS strongly recommended that sponsors be asked to conduct sonographic thick thickness compression studies to assure the drug product is not delivered into the bone if DAAAP concluded that an auto-injector could be labeled based on existing data.

On March 5, 2014, DAAAP presented their recommendations for labeling NAI for use in all pediatric patients ages birth to 17 years to the PeRC. The PeRC concluded that, labeling NAI for use in all pediatric populations was reasonable, but advised that Division should consider requiring the sponsor to conduct a safety study under FDAAA to ensure that the autoinjector can be used safely in the youngest pediatric patients. The PeRC also recommended that labeling clearly describe the safety concerns related to accidental penetration of bone for small infants and children. The PeRC also agreed with the Division's plan to ensure that labeling clearly state that pediatric patients should seek medical care after administration of the product.

Subsequently, DAAAP sent an information request (IR) to the applicant, Kaleo, asking them to perform a literature search and review on naloxone dosing in pediatric patients to support the proposed fixed naloxone dose in all pediatric age groups. The applicant was also asked to provide an argument in support of the acceptability of the proposed needle length for NAI in pediatrics and to propose language for the pediatric section of the labeling

On March 3, 2014, the applicant responded to the IR. PMHS has been re-consulted to assist in evaluating the sponsor's submission and the proposed language for the labeling.

Discussion of Submission:

(b) (4)
The applicant asserts that the 0.4mg fixed dose of naloxone is appropriate for pediatric patients ages birth to < 17 years based on the following:

- Wide safety margin for naloxone
- Clinical consequences of not treating an opioid overdose
- Impracticality of delivering pediatric weight-based dosing for naloxone (as is currently recommended in the labeling of Narcan, the referenced drug) in the community setting.
- Ability of their product to safely deliver an intramuscular or subcutaneous dose.

The applicant declared that a single dose of 0.4 mg provides at least 0.01mg/kg dose for patients weighing 60 to 170 pounds. A 0.4 mg dose provides between 0.02 and 0.04 mg/kg for pediatric patients weighing down to 20 pounds. A pediatric patient weighing 9 pounds would receive a dose of 0.1mg/kg. Furthermore the applicant cites AAP guidelines which state that doses up to 0.4 mg/kg and constant infusions of 0.16mg/kg/hr (for 5 days) have not been associated with naloxone related adverse events. The applicant believes that the 0.4mg dose will deliver doses ranging from 0.01mg/kg to 0.1mg/kg, and is consistent with current labeling for Narcan for the treatment of opioid overdose in pediatric patients. The applicant asserts that despite the fact that the NAI product will provide a dose to neonates that is slightly higher than that which is in the currently approved labeling for Narcan, the applicant believes the dose delivered (estimated to be 0.12 mg/kg/dose for a 7.5 pound (\approx 3.3 kg) female and 0.11 mg/kg/dose for an 8 pound (\approx 3.6 kg) male newborn is still below doses deemed to be safe in prior clinical studies and case reports for naloxone in infants.

Reviewer Comment:

The sponsor's plan appears reasonable. However, the data should still be interpreted with caution.

(b) (4)

Two NAI devices will be distributed with each prescription. If both products are administered to a patient, a total of 0.8 mg will be administered to a pediatric patient. There are published data that appear to support the safety of this dose. However, there may be questions regarding the efficacy of the dose especially in the older pediatric patients. Notably current dosing recommendations for adults stated that an initial dose of 0.4 mg to 2mg may be administered intravenously. The approved labeling for Narcan states that for "Narcotic-Induced Depression", the usual initial dose is 0.01mg/kg body weight administered I.V., I.M, or S.C. This dose may be repeated in accordance with adult administration guidelines for post-operative narcotic depression. Although the labeling for Narcan has separate recommendations for

narcotic overdose and post-operative narcotic depression, the presentation and management of these two conditions are similar.

As stated previously, the “Pediatric Use” section is not consistently presented in all generic labeling for naloxone hydrochloride products. Some naloxone product labeling also contain limitations for use and the Hospira naloxone product labeling states that the AAP does not endorse subcutaneous or intramuscular administration in opiate intoxication since absorption may be erratic or delayed. (Refer to DARRTS document 3461575, PMHS review dated February 27, 2014, under IND 112292 for additional details.) Based upon review of the generic labeling for naloxone hydrochloride products, practice guidelines from the American Academy of Pediatrics, information from the Substance Abuse and Mental Health Services Administration, and data from studies conducted with naloxone, there appears to be a wide margin of safety for naloxone. Data leading to the initial approval of naloxone in pediatric patients were based on review of 15 clinical studies (controlled and uncontrolled) in which neonates and children received parental naloxone in doses ranging from 0.005 mg/kg to 0.01 mg/kg. Guidelines and resources from the American Academy of Pediatrics and the American Association of Poison Control Centers recommend the administration of initial doses of naloxone up to 2 mg, which may be repeated if necessary to achieve the desired effect.^{1,2} Therefore, the sponsor’s proposed dose appears to be supported by sufficient safety information.

Given the wide range of doses used and documentation of cases where multiple dose administrations are required to achieve the desired effect, the applicant’s proposed initial dose may be too low to be effective in some patients or situations. Given the lack of controlled data from clinical trials and/or pharmacodynamic data with this application, questions regarding the most effective dose remain unanswered. As stated in the previous consult, with the increasing number of opioid overdoses over the past years, PMHS agrees there is an immediate public health benefit for this product.³ Given the safety margin in pediatric patients, and existing approved labeling supporting a dose of 0.01 mg/kg; the need for an easily administered naloxone device outweighs the need for additional dosing data prior to approval. Despite the potential for an initial dose to be ineffective in some patients, the overall efficacy of the proposed dose has been established and dosing of naloxone is based on achievement of a clinical response. Therefore, the currently proposed dose and plan to provide instructions for a second dose are reasonable. The Division may consider asking the sponsor to collect additional use and efficacy data, in the post-market setting.

The applicant also provided data to support their claims related to the difficulty of achieving precision and accuracy if required to develop a device that would allow for weight-based dosing regimens in the out-of-hospital setting. Root cause analyses have demonstrated that drug administration errors occurred due to cognitive, procedural, affective, and teamwork errors. The applicant asserts that the fixed dose NAI product may prevent weight-based dosing errors in both EMS and laypersons.

Finally the applicant states that the NAI product uses a nominal exposed needle length of 0.5 inches to deliver their product subcutaneously or intramuscularly. To address the

potential for over-penetrating the intramuscular space the applicant cited CDC recommendations needle lengths for injections into the anterolateral aspect of the thigh. The CDC recommendations are provided in the chart below reproduced from the applicant's submission:

Table 1: CDC recommendations for Intramuscular Injection into the Anterolateral Thigh Muscle of Pediatric Patients

Age Group	Needle Length (inch)	Technique
Newborn (first 28 days)	5/8"	90° to skin and spread skin if necessary
Infant (1 – 12 mths)	1"	
Toddler (1 – 2 yr)	1 – 1 ¼"	
Children (3 – 18 yr)	1 – 1 ¼"	

Source: Table 2 Applicant's submission dated March 10, 2014

The applicant also states that because naloxone may be given subcutaneously or intramuscularly under-penetrating the muscle space is not a concern.

Reviewer Comment:

The applicant's argument appears reasonable. CDC recommendations on immunizations state that, "A decision on needle size and site of injection must be made for each person on the basis of the size of the muscle, the thickness of adipose tissue at the injection site, the volume of the material to be administered, injection technique, and the depth below the muscle surface into which the material is to be injected." Since, appropriate needle length depends on age and body mass, concerns about the needle length would be most applicable to the youngest pediatric population and those with minimal subcutaneous fat. According to CDC recommendations, "If the subcutaneous and muscle tissue are bunched to minimize the chance of striking bone, a 1-inch needle is required to ensure intramuscular administration in infants aged ≥ 1 month. For the majority of infants, a 1-inch, 22- to 25-gauge needle is sufficient to penetrate the thigh muscle. For neonates (first 28 days of life) and preterm infants, a 5/8-inch needle usually is adequate if the skin is stretched flat between the thumb and forefinger and the needle is inserted at a 90-degree angle to the skin." The applicant's 0.5 inch needle appears to be acceptable.⁴ However, as stated in our previous consult, there is a precedent for other auto-injectors (i.e. Twinject and AdrenaClick devices used to administer epinephrine), whereby the applicant was asked to include a pharmacodynamics and pharmacokinetic modeling evaluation along with a tissue thickness sonographic study. The purpose of the tissue thickness sonographic study was to assess the safety of the applicant's proposed needle length and to ensure that the device did not inject drug substance or debris into the bony tissue. DAAAP may consider a similar approach for the naloxone products post-marketing.

Applicant's Proposed Labeling Changes



Reviewer Comment:

The applicant has not proposed language for Section 8.4.

DISCUSSION OF PEDIATRIC USE LABELING

The “Pediatric Use” subsection should clearly describe what is known and unknown about the use of the drug in pediatric patients, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with approved pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted (see Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling). The code of federal regulations (21 CFR 201.57(c)(9)(iv)) describes the appropriate pediatric use statements to include in labeling based on findings of safety and effectiveness in the pediatric population. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling must contain either the following statement or a reasonable alternative:

“The safety and effectiveness of (drug name) have been established in the age groups ___ to ___ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population.”

The following revisions to the sponsor’s proposed labeling are recommended to strengthen or clarify the language presentation. Medical Officer comments are provided in *italics*. The sponsor’s proposed revisions are noted with ~~strikeouts~~ for deletion of language and underlining for the addition of language. (Note: Excerpts from the labeling that are relevant to pediatrics are reproduced in this review. The reviewer defers to the Patient Labeling Team for recommendations to Section 17 of the labeling. However PMHS strongly recommends that information in the patient counseling section clearly state that EMS (911) should be immediately contacted once the medication is administered.)

PMHS will participate in labeling meetings that occur within the Division from now until the time of approval. Final labeling is subject to negotiations with the applicant and may not fully reflect changes suggested here. See the final approved labeling in DARRTS, which is appended to the approval letter. .

REVIEW OF LABELING AND PMHS RECOMMENDATIONS

Note: The tradename EVZIO is used throughout the labeling recommendations to represent the proposed NAI product.

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----DOSAGE AND ADMINISTRATION-----



Reviewer Comments:

Since the product is to be labeled for all pediatric populations,  (b) (4)



1 INDICATIONS AND USAGE

EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

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

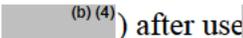
EVZIO is not a substitute for immediate medical care.

Reviewer Comment:

The proposed indication appears reasonable and consistent with prior PMHS recommendations.

2 DOSAGE and ADMINISTRATION

Important Administration Instructions

- EVIZO is for intramuscular and subcutaneous use only.
- Visually inspect EVZIO through the Viewing Window for particulate matter and discoloration prior to administration. Do not administer unless solution is clear and container is undamaged.
- Seek  (b) (4) medical care  (b) (4) after use  (b) (4)



- [REDACTED] (b) (4)

Because treatment of opioid overdose must be performed by someone other than the [REDACTED] (b) (4) patient, instruct the prescription recipient to inform those around them about the presence of EVZIO and the *Instructions for Use*.

[REDACTED] (b) (4) they receive a prescription for EVZIO. Provide the following instructions to the patient or caregiver:

- EVZIO must be administered according to the printed instructions on the device label OR the electronic voice instructions (EVZIO contains a speaker that provides voice instructions to guide the user through each step of the injection). If the electronic voice instruction system [REDACTED] (b) (4) operate properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions.
- [REDACTED] (b) (4)

Upon actuation, EVZIO automatically inserts the needle intramuscularly or subcutaneously, delivers 0.4 mg naloxone hydrochloride injection, and retracts the needle fully into its housing. Post injection, the black base locks in place, a red indicator appears in the viewing window, and electronic visual and audible instructions signal that EVZIO has delivered the intended dose of naloxone hydrochloride.

2.2 Dosing Information [REDACTED] (b) (4)

Administer the initial dose of EVZIO to adult or pediatric patients intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary and seek emergency medical assistance. Administer EVZIO as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death. If the desired response is not obtained after 2 or 3 minutes, another EVZIO dose may be administered. If there is still no response and additional doses are available, additional EVZIO doses may be administered every 2 to 3 minutes until emergency medical assistance arrives.

[REDACTED] (b) (4)

[REDACTED]

Reviewer Comment:

This section is difficult to read and contains several redundancies which may be edited for brevity.

Section 5 Warnings and Precautions

Reviewer Comment:

The applicant originally did not propose language related to opioid withdrawal for the labeling. PMHS notes that the primary reviewer has proposed preliminary language for this section. PMHS recommends to the following language to be consistent with prior recommendations related to opioid withdrawal.

5.3 Precipitation of Severe Opioid Withdrawal

The use of EVZIO in patients who are opioid dependent may precipitate an acute opioid withdrawal syndrome characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In the neonate, opioid withdrawal syndrome may also include: central nervous system excitability (e.g. convulsions and hyperactive reflexes), vasomotor signs, excessive crying, and gastrointestinal symptoms. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts. [Instructions for Patients (17) and Instructions for Use]

8.4 Pediatric Use

 (b) (4)

Reviewer Comment:

The dosing information should be included in the Dosage and Administration section of labeling and  (b) (4). However, the basis for the pediatric approval should be placed in this section to be consistent with 21 CFR 201.80. Safety and effectiveness of this product is based upon experience in adults and use in pediatrics. PMHS proposes the following language:

The safety and effectiveness of naloxone hydrochloride autoinjector (for intramuscular and subcutaneous use) have been established in pediatric patients for suspected complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic narcotics. Use of naloxone in pediatric patients is supported by evidence from adequate and well-controlled studies of naloxone in adults with additional data from 15 clinical studies (controlled and uncontrolled) in which neonates and pediatric patients received parental naloxone in doses ranging from 0.005mg/kg to 0.01mg/kg. Safety and effectiveness are also supported by safe use of other naloxone products in the post-marketing setting as well as data available in the medical literature and clinical practice guidelines.

Absorption of naloxone following subcutaneous or intramuscular administration in pediatric patients may be erratic or delayed. Even when the opiate -intoxicated child responds dramatically to naloxone hydrochloride injection, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized. In opioid-dependent pediatric patients, (including neonates), administration of naloxone may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts. (Section 5.3 Warnings and Precautions) Careful observation of the administration site for evidence of residual needle parts and/or signs of infection is also warranted. (Section 2.1 Dosage and Administration)

References

-
- ¹ American Academy of Pediatrics. Drugs for pediatric emergencies. *Pediatrics*. 1998;101:e13.
- ² Watson WA, Litovitz TL, Rodgers GC Jr, et al. 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *American Journal of Emergency Medicine*. 2005;23:589-666
- ³ Green JL, Desel H, Milanesi G, Sesana F, Brown JA, Gunja N, Kupferschmidt H, et al., “Unintentional pediatric opioid exposures as reported to the Global Toxicsurveillance Network (GTNet) from 2008 - 2010.” May 2013 Meeting of the International Congress of the European Association of Poisons Centres and Clinical Toxicologists, Copenhagen Denmark. Summary available at <http://www.radars.org/Portals/1/ConferenceAbstracts/Green-et-al-EAPCCT-2013.pdf> .
- ⁴ Kroger AT, Sumaya CV, Pickering LK, Atkinson, National Center for Immunization and Respiratory Diseases. “Recommendations of the Advisory Committee on Immunization Practices (ACIP)” Jan. 28, 2011 60(RR02);1-60. Accessed March 12, 2014 at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm>.

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/s/

ERICA WYNN
03/29/2014

LYNNE P YAO
03/30/2014

**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: March 28, 2014

To: Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

L. Shenee' Toombs, 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: EVZIO (naloxone hydrochloride injection), for intramuscular or subcutaneous use

Application Type/Number: NDA 205787

Applicant: kaleo, Inc.

1 INTRODUCTION

On December 20, 2013 kaleo, Inc. submitted for the Agency's review the final portions of a rolling submission for New Drug Application (NDA) 205787 for EVZIO (naloxone hydrochloride injection). Also on December 20, 2013, kaleo, Inc. notified FDA of the change of ownership of NDA 205787 from Intelliject VA, Inc. to kaleo, Inc. EVZIO is a pre-filled auto-injector with the proposed indication for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

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 Anesthesia, Analgesia, and Addiction Products (DAAAP) on March 26, 2014, and March 19, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for EVZIO (naloxone hydrochloride injection).

2 MATERIAL REVIEWED

- Draft EVZIO (naloxone hydrochloride injection) PPI received by DMPP on March 26, 2014.
- Draft EVZIO (naloxone hydrochloride injection) PPI received by OPDP on March 19, 2014.
- Draft EVZIO (naloxone hydrochloride injection) Prescribing Information (PI) received by DMPP on March 26, 2014.
- Draft EVZIO (naloxone hydrochloride injection) Prescribing Information (PI) received by OPDP on March 7, 2014.
- Draft EVZIO (naloxone hydrochloride injection) Trainer Instructions for Use (IFU) received by DMPP on March 26, 2014
- Draft EVZIO (naloxone hydrochloride injection) Trainer Instructions for Use (IFU) received by OPDP on March 19, 2014
- Draft EVZIO (naloxone hydrochloride injection) IFU received by DMPP on March 26, 2014.
- Draft EVZIO (naloxone hydrochloride injection) IFU received by OPDP on March 19, 2014.

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. In our review of the PPI and IFU's the target reading level is at or below an 8th grade 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 APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU's document using the Verdana font, size 10 and 11 respectively.

In our collaborative review of the PPI and IFU's we have:

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

4 CONCLUSIONS

The PPI and IFU's 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's 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's.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
03/28/2014

LATOYA S TOOMBS
03/28/2014

BARBARA A FULLER
03/28/2014

LASHAWN M GRIFFITHS
03/28/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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:	March 27, 2014
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 205787
Product Name and Strength:	Evzio (naloxone hydrochloride injection, USP), 0.4 mg/0.4 mL
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Kaleo (previously Intelliject)
Submission Date:	February 27, 2014
OSE RCM #:	2013-1727
DMEPA Primary Reviewer:	Vicky Borders-Hemphill, Pharm.D
DMEPA Team Leader:	Irene Z. Chan, Pharm.D., BCPS

1 REASON FOR REVIEW

This review evaluates the acceptability of the purpose statement, “for Opioid Emergencies”, proposed throughout labels and labeling for Evzio (naloxone hydrochloride injection, USP), from a medication error perspective as requested by DAAAP. This review also provides additional recommendations for the revised labels and labeling submitted by the Applicant on January 2, 2014.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant currently uses the statement, “(b) (4)”, throughout all proposed Evzio labels and labeling. During labeling meetings, several review team members expressed concern about whether this statement may cause confusion for laypersons, resulting in hesitation to use the product. This concern prompted an internal study, conducted by the Risk Communication Staff (RCS) in partnership with the Office of Communications (OCOMM), to conduct informal message testing of plain language descriptions of an indication statement that might be included on the carton labeling of a product such as Evzio. Additionally, the Applicant was sent two separate information requests to gather information regarding their rationale for use of the statement “(b) (4)”, including a detailed history regarding the evolution of this statement and any testing conducted regarding the statement. We also referred to several additional resources to inform our decision regarding the acceptability of the

purpose statement, “ (b) (4)”, proposed throughout labels and labeling, from a medication error perspective (see Appendix F).

Our evaluation of the RCS/OCOMM study report determined the results were inconclusive and could not be applied to the general population. It was unclear who the twelve subjects in the study were, and whether they could be considered representative of the general population. Additionally, the study did not evaluate whether there was any difference in understandability of messaging based on previous exposure to the product. We postulate that it is likely that caregivers or family members that will use Evzio will already have been informed of its existence and will have a basic understanding of the product and its intended use. It is unclear what effect this could have on understandability of messaging regarding when to use Evzio.

We also assessed the Applicant’s response to information requests. The Applicant stated that the term “Opioid” was chosen to encompass all drugs (i.e., illicit drugs containing opioids, other medications containing opioids and legitimate pain medications) that might result in the use of Evzio. Additionally, the Applicant indicated that responses to questions asked of subjects in the human factors validation study indicate that subjects commonly described the scenario using the terms “overdose” and “emergency” with similar frequency. The Applicant decided to remove the word

(b) (4) since it may (b) (4)
Additionally, the Applicant indicated that (b) (4)
.”

The purpose statement located on the device label, the outer case labeling, carton labeling, and other patient labeling will need to be understood by a layperson end user. The word “opioid” is a term understood by health care professionals, but laypersons may not be familiar with all of the various drugs included in this group of products. We considered whether listing specific drugs (i.e., morphine, fentanyl, oxycodone, hydrocodone, etc) would be appropriate; however, this may be too restrictive and suggest to users that Evzio can only be used with the drugs listed on the carton. We also considered whether the word “emergencies” is too broad or open to interpretation. During the course of our research, we found that the term “opioid intoxication” is currently used by the U.S. National Library of Medicine, National Institutes of Health’s Medline Plus website. However, we do not currently have data to support that this term would be better understood by the general public as compared to opioid emergencies. Since the Applicant stated that responses to questions asked of subjects in the human factors validation study indicate that subjects commonly described the scenario using the terms “overdose” and “emergency” with similar frequency, a more descriptive statement similar to “for opioid emergencies such as overdose” might be preferable. If feasible, we recommend the Applicant conduct further testing of this and other

alternative messages in a labeling comprehension study prior to approval of this product. DMEPA will monitor for any postmarketing reports of confusion related to the final messaging, inappropriate use, or omission for this product.

We note that the statement “seek emergency medical attention” is only on the device label which is covered by the outer case and is not seen until the outer case is removed. We recommend the device outer case label includes the statement to seek emergency medical attention to prompt the end user to perform this important task in addition to administering the product. Additionally, this statement should also be added prominently to the carton labeling (see Section 4.2 Recommendations for the Applicant).

4 CONCLUSION & RECOMMENDATIONS

Our review concludes that improvements can be made to the labels and labeling to ensure the safe use of this product. There is inadequate data to support substantive changes to the Applicant’s proposed statement [REDACTED] (b) (4); however, based on the totality of information reviewed, we recommend DAAAP consider revising the statement to read “for opioid emergencies such as overdose”. We provide recommendations for the Applicant in Section 4.2 below.

If you have further questions or need clarifications, please contact Lisa Skarupa, project manager, at 301-796-2219.

4.1 RECOMMENDATIONS FOR THE DIVISION

- A. Since the Applicant stated that responses to questions asked of subjects in the human factors validation study indicate that subjects commonly described the scenario using the terms “overdose” and “emergency” with similar frequency, a more descriptive statement similar to “for opioid emergencies such as overdose” should be considered. If feasible, we recommend the Applicant conduct further testing of this and other alternative messages in a labeling comprehension study prior to approval of this product.

4.2 RECOMMENDATIONS FOR THE APPLICANT

- A. Outer Case Labels
 - 1. Add the statement “Seek Emergency Medical Attention” on the principal display panel to ensure that this important information is visible and helps to prompt the user to seek medical attention. To accommodate this statement, consider shortening the shaft of the arrow or shrinking the arrow overall.
 - 2. The statement [REDACTED] (b) (4) is inadequately prominent underneath the white highlighted box in the lower third of the principal display panel. Consider alternate means for presenting this information (i.e., moving statement up into white highlighted box) to ensure it is easily visible.

B. Carton Labeling

1. Add the statement “Seek Emergency Medical Attention” on the principal display panel to ensure that this important information is visible and helps to prompt the user to seek medical attention.
2. Move the statement [REDACTED]^{(b) (4)}” from the side panel to the principal display panel for increased prominence.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

Appendix A. Product Information

Table 2 presents relevant product information for Evzio that Kaleo submitted on January 22, 2014.

Table 2. Relevant Product Information for Evzio	
Active Ingredient	naloxone hydrochloride injection, USP
Indication	(b) (4)
Route of Administration	intramuscular or subcutaneous
Dosage Form	injection
Strength	each NAI delivers 0.4 mg naloxone hydrochloride (0.4 mL)
Dose and Frequency	injection once into the anterolateral aspect (outer) of the thigh, through the clothing if necessary; if the desired degree of counteraction and improvement in respiratory function is not obtained, after 2-3 minutes, another dose may be administered. (b) (4)
How Supplied	carton containing two pre-filled, single use naloxone auto-injectors (NAI) and a single NAI trainer;
Storage	Controlled room temperature 59°F to (b) (4) °F. Temperature excursions permitted between 39°F and 104°F. Do not refrigerate or freeze.
Container Closure	devices are equipped with an electronic voice prompt system that provides audible instructions for use using voice commands and beeps and visual cues (red/green LED lights)

APPENDIX C. PREVIOUS DMEPA REVIEWS

In OSE review 2013-1727, dated December 11, 2013, we initially reviewed container labels, carton labeling, and Information and Instructions for use leaflets for the device and the trainer.

In OSE review 2013-1727 dated February 4, 2014, we reviewed label and labeling revisions that addressed our December 11, 2013 recommendations and found the implementation of those recommendations acceptable. We also reviewed new labeling for the Trainer outer case from the second manufacturing facility and the carton labeling for the new packaging configuration and for a professional sample and found them acceptable. This review also provided our recommendations for the Package insert (submitted January 22, 2014) to DAAAP.

We reviewed revised labels and labeling for the Trainer for Evzio submitted by the Applicant on February 27, 2014, against our recommendations in OSE Review 2013-1727, dated February 4, 2014. We communicated to DAAAP in an email dated February 28, 2014, that revisions to the labels and labeling for the Trainer for Evzio were acceptable from a medication error perspective.

APPENDIX F. Sources for Purpose Statement Terminology

F.1 Methods

1. We searched medical websites for the term “opioid” to determine whether alternate wording has been used on patient centered websites.
2. We reviewed the study results report, submitted by the Risk Communication Staff (RCS) in partnership with the Office of Communications (OCOMM), on informal message testing of plain language descriptions of an indication statement that might be included on the carton labeling of a product such as Evzio. The study reported the responses from 12 individual telephone interviews with FDA employees from FDA’s Message Testing Network. The study assessed the following four label statements: “for the treatment of opioid overdose”, “for opioid emergencies”, “use to reverse harmful effects from opioids”, and “antidote for opioid overdose”.
3. We sent two information requests to the Applicant during the review process to clarify the evolution of the messages “(b) (4)” and “(b) (4)” since the validation usability testing. Early device and outer carton labels used “(b) (4)” and “(b) (4)” statements.

F.2 Results

The U.S. National Library of Medicine, National Institutes of Health’s Medline Plus is a website (www.nlm.nih.gov) intended for use by laypersons and uses the term “opioid intoxication” with symptoms of opioid intoxication defined as breathing problems (breathing may stop), extreme sleepiness or loss of alertness, and small pupils.

Based on the results of the RSC/OCOMM study, the RSC’s recommendations included:

- Form a new label statement that uses the best words from the tested statements “for the treatment of opioid overdose”, “for opioid emergencies”, “use to reverse harmful effects from opioids”, and “antidote for opioid overdose”.
- Avoid vague terminology such as “emergencies” and “harmful effects”
- Consider listing opioid products somewhere on the carton
- Consider using a large font and including an autoinjector graphic for instant recognition

In emails dated October 23, 2013, and March 19, 2014, the Applicant responded to our information requests regarding their decision process for changes to the purpose statement as follows:

Response pertaining to terms used in Human Factors User Interface Design Validation Study IJ-1025SER-03O:

The use scenario for this study was intended to represent the worst-case scenario and

therefore involved no pre-training/education of subjects.

The participant briefing script utilized for this study included the following combination of phrases to describe the use scenario:

- “overdosed on a prescription pain medication”
- “overdose”
- “overdoses on a pain medication”
- “prescription medication overdose”
- “pain medication overdose”
- “pain medication overdose emergency”

The term “pain medication” was used because it accurately described the use scenario examined in this study (i.e., a patient taking a legitimate prescription opioid for the treatment of pain).

Test product labels utilized in the study stated “For Opioid Overdose Emergencies” as the purpose for NAI.

- The term “Opioid” was chosen to encompass all drugs (i.e., illicit drugs containing opioids, other medications containing opioids and legitimate pain medications).
- The term “Overdose” was chosen because it is defined as “too great a dose (as of a therapeutic agent)” or “a lethal or toxic amount (as of a drug)”.
- The term “Emergencies” was chosen because it is defined as “an unexpected and usually dangerous situation that calls for immediate action”.

Responses to post-simulation questions asked of subjects in the study indicate that subjects commonly described the scenario using the terms “overdose” and “emergency” with similar frequency.

Response to "Overdose" Text Removal

The rationale for changing “For Opioid Overdose Emergencies” to “For Opioid Emergencies” on the NAI label is that opioid-related, life-threatening respiratory depression and/or central nervous system depression and even death can occur at recommended doses, not just at doses greater than recommended (i.e., overdose). Leaving “Overdose” in the description may create a perception that limits the prescription of NAI to only those patients whom the physician believes are

- illicit drug users or
- abusing opioids or
- likely will take more than the prescribed amount of an opioid.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis¹, we reviewed the following Evzio labels and labeling submitted by Kaleo on January 2, 2014.

- Container label: revised Evzio device labels
- Container label: revised Evzio outer case labels
- Carton labeling for two Evzio devices and one Trainer
- Package Insert submitted January 22, 2014

G.2 Label and Labeling Images

Revised Container Labels for Device submitted January 2, 2014

NAI Device Label



Code 39 barcode reads 1607

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¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

BRENDA V BORDERS-HEMPHILL
03/27/2014

IRENE Z CHAN
03/27/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	EVZIO (naloxone hydrochloride injection), for intramuscular or subcutaneous use
Applicant	Kaleo, Inc.
Application/Supplement Number	NDA 205787
Type of Application	Original
Indication(s)	For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
Office/Division	ODEII/DAAAP
Division Project Manager	Diana Walker
Date FDA Received Application	December 20, 2013
Goal Date	June 20, 2014
Date PI Received by SEALD	March 26, 2014
SEALD Review Date	March 26, 2014
SEALD Labeling Reviewer	Abimbola Adebowale
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *HL length is > ½ page. DAAAP will grant waiver in approval letter.*

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *The horizontal line separating the HL from the TOC is missing. The horizontal line separating the TOC from the FPI is also missing. Insert both horizontal lines.*

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *1. All the headings in HL are not presented in the center of a horizontal line. Center them. 2. Each horizontal line does not extend over the entire width of the column as shown in Appendix A for the following headings: Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Warnings and Precautions and Adverse Reactions.*

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

Selected Requirements of Prescribing Information

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Selected Requirements of Prescribing Information

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

Selected Requirements of Prescribing Information

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *The bolded revision date at the end of HL should read as “Revised: 3/2014” instead of “Revised: X/2014.”*

Contents: Table of Contents (TOC)

Selected Requirements of Prescribing Information

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: *Subsection heading “5.3 Precipitation of Severe Opioid Withdrawal5.4” in the TOC does not match subsection heading 5.3 “Precipitation of Severe Opioid Withdrawal” in the FPI. Match the TOC and FPI subsection headings.*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION

Selected Requirements of Prescribing Information

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: 1. The subsection heading currently written as “8.3 (b) (4)” in the FPI should read as “8.3 Nursing Mothers” as shown in the table above. 2. The subsection heading currently written as “12.3 Pharmacokinetics” should read as “12.3 Pharmacokinetics” (i.e. insert a space between).

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)]”.

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

Selected Requirements of Prescribing Information

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

N/A 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ABIMBOLA O ADEBOWALE
03/26/2014

ERIC R BRODSKY
03/26/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: March 26, 2014

To: Diana Walker, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 205787
OPDP labeling comments for EVZIO (naloxone hydrochloride injection),
for intramuscular or subcutaneous use
Labeling Review

OPDP has reviewed the proposed package insert (PI) and carton/container labeling for EVZIO (naloxone hydrochloride injection), for intramuscular or subcutaneous use (Evzio) that was submitted for consult on January 13, 2014. Comments on the proposed PI are based on the version sent via email from Diana Walker (RPM) on March 26, 2014 entitled "Proposed draft USPI 26Mar14.doc"

Comments regarding the PI are provided on the marked version below.

We have no comments on the draft carton/container labeling accessed from the following EDR location, \\CDSESUB1\evsprod\NDA205787\205787.enx

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LATOYA S TOOMBS
03/26/2014

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 10, 2014

TO: Bob Rappaport, MD
Director,
Division of Anesthesia, Analgesia, and Addiction
Products
Office of Drug Evaluation II

FROM: Chase Bourke, Ph.D.
Pharmacologist, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Charles Bonapace, Pharm.D.
Acting Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Acting Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering NDA 205-787, Naloxone
Autoinjector, sponsored by Kaleo Inc., USA

At the request of the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), the Division of Bioequivalence and GLP Compliance (DBGLPC) inspected the following study:

IJ-900DV-030: "A Randomized, Single-Blind, Two-Sequence, Two-Period Comparative Bioavailability Study of Two Naloxone Hydrochloride Products in Healthy Human Volunteers"

Clinical:

The inspection of the clinical portion of the study was conducted by Brandon Mariner (ORA) during March 4-7, 2014 at

**PAREXEL, Harbor Hospital, 7th Floor, 3001 South Hanover Street,
Baltimore, Maryland 21225 (PAREXEL).** No significant issues were
observed and no Form FDA 483 was issued.

Analytical:

The inspection of the analytical portion of the study was
conducted by Corey Reno (ORA), Charles R. Bonapace, Pharm.D.
(OSI), and Chase H. Bourke, Ph.D. (OSI) during (b) (4)
(b) (4) at (b) (4). No Form
FDA 483 was issued.

Conclusions:

Following evaluation of the inspectional findings, the DBGLPC
reviewers recommend that the data from the clinical and
analytical portions of study IJ-900DV-030 are acceptable for
Agency review.

Chase H. Bourke, Ph.D.
GLP Branch, DBGLPC, OSI

Charles R. Bonapace, Pharm.D.
GLP Branch, DBGLPC, OSI

Final Classification:

NAI - (b) (4)
FEI: (b) (4)

NAI - PAREXEL, Baltimore, MD
FEI: 3005445577

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Bonapace/Mada/Bourke/Dejernett/
CDER/OND/Walker/Rappaport
CDER/OTS/OCP/Xu/Qiu
ORA/DET-DO/Reno
ORA/BLT-DO/Mariner
Draft: CHB 03/10/2014
Edit: CRB 03/10/2014

Page 3 - NDA 205-787, Naloxone Autoinjector, sponsored by
Kaleo Inc., USA

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical
Sites ██████████ (b) (4) NDA 205-787_Naloxone Autoinjector
Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory
Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/PAREXEL, Baltimore, MD/NDA 205-787_Naloxone Autoinjector

File: BE6660; O:\BE\EIRCOVER\205787 kal nal.doc
FACTS: 8742520

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/s/

CHASE H BOURKE
03/10/2014

CHARLES R BONAPACE
03/10/2014

WILLIAM H TAYLOR
03/11/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: February 18, 2014

TO: Diana Walker, DAAAP/ODEII/OND/CDER/OMPT. WO-22
Room 3240 Diana.Walker@fda.hhs.gov

Parinda Jani, DAAAP/ODEII/OND/CDER/OMPT. WO-22 Room
3166 Parinda.Jani@fda.hhs.gov

Office of combination products at combination@fda.gov

Juandria Williams, GDMAB/DGMPA/OMPQ/OC/CDER/OMPT.
WO-51 Room 4216 Juandria.Williams@fda.hhs.gov

Through: Carl Fischer, Chief, REGODB/DMQ/OC/CDRH/OMPT. WO-66,
Room 3526

From: M. Isabel Tejero, QSWGL/DMQ/OC/CDRH/OMPT. WO-66,
Room 3554. Isabel.Tejero@fda.hhs.gov

Applicant: Kaléo Pharma Inc. (formerly Intelliject)
111 Virginia St, Suite 300
Richmond, VA 23229
FEI # 3007135538

Application # NDA 205787 (IND 112292)

Product Name: Evzio, a Naloxone Auto-Injector (NIA), containing 0.4 mg of
naloxone hydrochloride injection, USP

Consult Evaluate the firm's response to the deficiency letter sent by CDER
Instructions: to Kaleo on January 22, 2014.

This memo is an extension to the memo provided to CDER in response to the original consult and dated January 21, 2014. This document includes the evaluation of the firm's response to the deficiency letter sent by CDER to Kaleo on January 22, 2014. For

additional information regarding the initial evaluation of the application, see the attached memo for the original consult.

(b) (4)

This is a single dose injector (figure 1) with a dosage of 0.4 mg (0.4 mg/ 0.4 mL) naloxone hydrochloride injection, USP.

(b) (4)
It may be used by laypersons or caregivers in the out-of-hospital, non-healthcare environment.

EVALUATION OF THE FIRM RESPONSE TO THE IDENTIFIED DEFICIENCIES

The documentation submitted by Kaleo in response to the deficiency letter sent on January 22, 2014, regarding NDA 205787 has been evaluated. Below are the evaluations of the firm's responses to each deficiency.

1. Following the requirements of 21 CFR820.40, document controls, all procedures and documents provided to show compliance with the regulatory requirements under 21 CFR part 820 should be updated to reflect the firm's name change.

Evaluation of firm's response. The firm's response is adequate: Kaleo indicated via email that all procedures will be updated to reflect the name change from Intelliject, Inc. to Kaleo, Inc. Additionally, the firm will be attaching a cover letter reflecting the name change to all other documents (i.e. validation plans for the NAI, etc.).

2. Nonconforming product, 21 CFR 820.90 requirements. The following deficiency was found:
 - a. (b) (4)

Evaluation of firm's response. The firm's response is adequate: the revised procedure (b) (4)

3. Corrective or Preventive Actions (CAPA), 21 CFR 820.100 requirements, the following deficiencies were appreciated:
 - a. The procedures provided do not address how your firm's CAPA system is tied to its risk management program.

(b) (4)

- b. The procedures do not address how your firm will ensure that the Corrective and/or Preventive Action are effective and have not adverse effects on the product. Specifically, the procedures did not address the following requirements:

(b) (4)

(b) (4)

CDRH OFFICE OF COMPLIANCE RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of application NDA 205787, and the firm's response to the deficiency letter dated January 22, 2014, and has the following recommendations:

The desk review of application NDA 205787 has been completed, and there are no residual deficiencies.

Additionally, as conveyed in the previous memo, CDRH recommends that the (b) (4), and with FEI # (b) (4), be inspected for compliance with 21 CFR part 820, preferably before NDA 205787 is approved.

However, CDRH/OC would consider acceptable a post-market inspection of the (b) (4) due to the public health benefit of the rapid approval of Evzio naloxone autoinjector, and based on the adequate desk review and previous NAI inspections of two (b) (4), in (b) (4), which included an autoinjector pen with electronic components.

M. Isabel Tejero del Rio, MD, Ph.D.

Prepared: MITejero: 2/13/2014; 2/18/2014
Reviewed: CFischer: 2/18/2014

CTS No.: ICC1300133/S001
NDA 205787

Inspectional guidance

Firm to be inspected:



A comprehensive baseline Level 2 inspection is recommended focusing on Management controls, manufacturing including acceptance activities, CAPA and complaint handling.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Dr. M. Isabel Tejero del Rio
CSO
REGODB, DMQ, OC, CDRH, OMPT
Office of Compliance, WO66 RM 3554
Phone: 301-796-5322

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Dr. Carl Fischer
Chief
REGODB, DMQ, OC, CDRH, OMPT
WO-66, Room 3526
Phone: 301-796- 5770

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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

/s/

DIANA L WALKER

02/20/2014

CDRH consultative review entered into DARRTS for:
M. Isabel Tejero, QSWGL/DMQ/OC/CDRH/OMPT



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
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Date: February 6, 2014

From: Lana Shiu, M.D.

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To: Diane Walker

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Via: Keith Marin

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Subject: NDA 205787 Naloxone Autoinjector (NAI) Submitted by Kaleo

CDRH Tracking: ICC1300678

NAI is based on the same autoinjector platform as the EAI (epiCard/Auvi-Q (NDA 201739))which has the same user interface and operate using the same mechanical design, materials of construction, retraction features, LED feature and voice prompts/software. CDRH provided the engineering device consult on the autoinjector and its software during the review of EAI during the IND 76367 as well as during the NDA 201739 review process.

NAI is a single-use, personal use auto-injector that delivers 0.4 mg naloxone hydrochloride (HCl) via subcutaneous or intramuscular injection. NAI is a drug-device combination product containing a prefilled naloxone HCl Drug Constituent Component.

The Drug Constituent Component of NAI is a parenteral formulation that is filled into a Type I (b) (4) glass cartridge and enclosed by an (b) (4) plunger and (b) (4) lined crimp cap (i.e., primary container closure). The NAI parenteral formulation (b) (4) a listed drug product (International Medicinal Systems, Limited 2 mg/ 2mL (single dose disposable LUERJET prefilled syringe).

The Device Constituent Component of NAI is a (b) (4), needle-based system that delivers the prescribed dose of naloxone HCl into the user. When activated, NAI will inject a single dose of 0.4 mL (0.4 mg of naloxone HCl). NAI is designed to be a single-use device, so any residual parenteral formulation remaining in the device after injection of the dose cannot be utilized.

Intended Use

NAI is a single-use autoinjector for administration by lay-person or caregiver to a person experiencing opioid emergency.

Device Description

The Device Constituent Component of NAI is a compact, user-actuated, (b) (4) autoinjection system that delivers 0.4 mg naloxone hydrochloride injection, USP (1 mg/mL) through a needle into the patient once activated. The needle is fully retracted within the device housing following use.

In addition to labels that provide written instructions for use, NAI includes an enhanced instructions-for-use feature in the form of an electronic prompt system (also referred to as the "Intelliject Prompt System (IPS)") that provides audible instructions for use and visual cues to assist in guiding the user through the injection process.

The IPS is not intended to be the only instructions that the user should rely upon and the software for the electronic prompt system acts completely independent from the drug delivery functionality for the NAI.

Operating Principle



Naloxone Drug Container Closure system and Delivery Path

The Drug Cartridge container closure system for the naloxone drug product consists of a Type 1 (b) (4) glass Cartridge with an (b) (4) Plunger and an aluminium Crimp Cap lined with an (b) (4)

The septum of the lined Crimp Cap remains intact in the Cartridge Assembly within NAI. When the NAI is activated, the needle fully extends into the patient followed by the Crimp Cap end of the glass cartridge snapping down into the Cartridge Carrier and butt end of the Needle. The stopper then moves downward to expel the naloxone injection solution from the reservoir, through the Needle, and into the patient.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Prevention of Under/Over Dosing

The volume of naloxone solution dispensed is determined by the initial position of the Plunger within the Cartridge and the distance the Plunger moves after activation. (b) (4)

The Piston moves the Plunger after activation. (b) (4)

Under dosing is prevented by ensuring the Piston moves the full distance from the initial position to the top of the Cartridge Carrier after activation (b) (4)

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

Premature dosing during injection of the Needle is prevented because the Plunger will not depress until the Cartridge Carrier (including Needle) bottoms out within the housing thereby ensuring full needle extension into the patient prior to injection of the drug.

Premature retraction of the needle prior to full delivery of the drug dose is also prevented by design. The Cartridge Carrier (including needle) will not retract until the Piston and Plunger are fully depressed to their respective dosage delivery positions and the Piston is seated at the top of the Cartridge Carrier. (b) (4)

A summary of the operating principles for administration of an injection of naloxone using NAI are as follows:

1. Remove NAI from its outer case



2. Pull off RED safety guard



3. Place BLACK end AGAINST OUTER THIGH then PRESS FIRMLY for 5 seconds.



The electronic prompt system begins to provide audible and visual cues to guide the user through the above administration steps as soon as the device is removed from its outer case. This includes cueing a user “if ready to use, pull off red safety guard” and “To inject, place black end against outer thigh, then press firmly while holding in place for 5 seconds”, counting down “5...4...3...2...1” during activation, and providing dose confirmation with “injection complete, seek emergency medical attention.”

Once the user presses NAI against the injection site, a gas-powered activation mechanism causes needle insertion, naloxone hydrochloride injection, followed by needle retraction. This entire injection and retraction process takes less than five seconds.

Safety systems:

- Retractable needle system that:
 - will automatically inject the needle upon activation, fully deliver naloxone through the needle, and retract the needle into the housing once injection and dose delivery is complete;
 - cannot be deactivated and prevents finger/digit access to the needle before and after an injection; and
 - provides visual clues to confirm the injection is complete and the needle has retracted into the housing properly. Patients do not see the needle before, during, or after administration.
- An outer case that works as an activating switch (when removed) for the voice instructions.
- A RED safety guard that prevents accidental activation of the injection. The color red helps indicate the needle end of NAI as it is commonly associated with representing ‘danger’ or ‘energy’.
- Post-injection, the black base will lock into place, the electronic prompt system will indicate injection completion and instruct the patient to seek further medical assistance, the red safety guard cannot be replaced and the viewing window will be obscured with a red indicator (indicating that NAI has already been used and should be replaced).
- NAI outer case design that prevents a Trainer from being mistakenly placed in a NAI outer case.
- Trainer outer case design that prevents a NAI from being mistakenly placed in a Trainer outer case.
- The NAI outer case is designed to not be compatible with the similar form factor Auvi-Q[®] (marketed epinephrine auto-injector). NAI will not fit into the outer case of Auvi-Q and *vice versa*.

Sharps Injury Prevention Safety Feature

NAI contains several safety features designed to prevent hazards to the user before, during and after use. One of the key safety features is NAI’s sharps injury prevention feature (Retractable Needle). This feature includes the following attributes:

- Automatic activation of the Needle and penetration into the target site, injection of the drug through the Needle and dispersion into the target site, and retraction of the Needle in less than 5 seconds;
- The retracted Needle cannot be re-exposed;

- Visual cues, including a viewing window located on NAI, aid in providing the user with confirmation that the retractable Needle has functioned appropriately;
- The Retractable Needle retracts fully into the device housing; and
- The Retractable Needle prevents finger/digit access before and after injection.

The effectiveness of NAI's retractable needle user interface to prevent sharps injuries was validated through Intelliject Study INT0803 *epiCard Auto-Injector: Validation of Sharps Injury Prevention Feature & Simulated Use Study* during the development of Auvi-Q (NDA 201739). In this study 28 health care professionals (in accordance with FDA's 2005 Guidance: *Medical Devices with Sharps Injury Prevention Features*) inject an instructional model (an orange) 18 times (9 with wet hands and 9 with dry hands) using 18 different epinephrine auto-injectors (EAI). One subject completed 1 additional test using wet hands. The subjects and investigational staff recorded whether the injection of the needle was successful and the retractable needle functioned appropriately. All 505 epinephrine auto-injectors tested (100%) were successful in having the needle inject and successfully retract; therefore, the testing validated the sharps injury prevention feature for EAI, regardless of whether the subjects had wet or dry hands.

Review and Comments:

(b) (4)

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

Related Substances	Section 3.2.P.5.2.1 (ATM-8v3)	(b) (4)
Particulate Matter	USP	NMT (b) (4) μm and NMT (b) (4) μm per container
Sterility	USP	Conforms
Endotoxin	USP	NMT (b) (4) U/mg of Naloxone HCl
Activation Force	Section 3.2.D.5.2	(b) (4) lbs
Volume Dispensed		(b) (4) mL
Dispensing Time		(b) (4) seconds
Exposed Needle Length		(b) (4) (b) (4) in

The sponsor claims conformance to the following standards and provided test results according to the listed design attributes:

- [ISO 11608-1:2000](#) Pen-injectors for medical use -- Part 1: Pen-injectors -- Requirements and test methods
- [ISO 11608-2:2000](#) Pen-injectors for medical use -- Part 2: Needles -- Requirements and test methods
- [ISO 11608-3:2000](#) Pen-injectors for medical use -- Part 3: Finished cartridges -- Requirements and test methods

The sponsor conforms to the following IEC standards:

IEC/UL/CSA/EN 60601-1-1	Medical electrical equipment. General requirements for safety. Collateral standard. Safety requirements for medical electrical systems
IEC/UL/CSA/EN 60601-1-2	Medical electrical equipment - Part 1-2: General requirements for safety - Collateral standard: Electromagnetic compatibility - Requirements and tests

Description	References	Acceptance Criteria	Batch Tested/ Results
Volume Dispensed Test Report: (n=64)	ISO 11608-1	Volume Dispensed: (b) (4) mL	PASS (b) (4)
Environmental Exposure Test Report: Std Atm Test (6.1) (n = 60) Cool Atm Test (6.2) (n = 60) Hot Atm Test (6.3) (n = 60)	ISO 11608-1 Section 9.2.2	Volume dispensed will be measured on all devices following environmental exposure. Volume Dispensed: (b) (4) mL	PASS (b) (4)

Description	References	Acceptance Criteria	Batch Tested/ Results
Pre-Conditioning Test Report: Dry Heat Atm test (n =60) Cold Storage test (n = 59) Vibration test (n = 20) Free Fall test (n=30)	ISO 11608-1 IEC 60068-2-30 IEC 60068-2-6	Freedom from visual defects Volume Dispensed: (b) (4)	PASS (b) (4)
IEC Testing Report: Testing for the electronic prompt system component of NAI	ISO 11608-1 (Section 10) UL/IEC 60601-1-1 IEC 60601-1-2	Pass/Fail	PASS Batch - N/A

Description	References	Acceptance Criteria	Batch Tested / Results
Needle Bond Strength Test Method and Report: Design of Experiments study to establish UV cure intensity (W/cm ³) and exposure time. (N=51 tested after at different process conditions)	ISO 11608-2 (Section 11) IEC 60068-2-30	(b) (4)	PASS Batch - N/A

Description	References	Acceptance Criteria	Batch Tested / Results
Freedom From Leakage Test The cartridge shall be free from leakage at the plunger or the disc	ISO 11608-3, Section 5.5.	No leak occurs while a force of (b) (4) N is applied to plunger for (b) (4) min	PASS Batch # tested (b) (4) None of the tested units showed any leakage.

Description	References	Acceptance Criteria	Batch Tested/ Results
Plunger Break/Glide Force Test w/Drug Report Test method for determining the maximum compression force required to initiate and sustain movement of the siliconized plungers used in NAI.	ISO11608-3 Section 5.6	The initiating force shall not exceed (b) (4) N. The sustaining force shall not exceed (b) (4) N	PASS (b) (4)
Lubrication Visual inspection to ensure lubricant is not visible	ISO11608-3 Section 5.5	The lubricant shall not, under normal or corrected-to-normal vision, be visible as droplets of fluid on the outside or inside surfaces of the components.	Cartridges are tested by visual inspection to ensure compliance

Description	References	Acceptance Criteria	Batch Tested / Results
Needle Injection Force Test Report: Test method for determining the amount of force NAI creates during an injection. (n=20)	FDA Draft Guidance on Injectors (April 29 2009)	> (b)(4) lbf	PASS (b)(4)
Cartridge Snap Force Test Report: Test method for determining the amount of force it takes to snap the drug cartridge crimp cap down past the snap ring on the needle hub. (n=30)		FIO	Batch - N/A (b)(4)
Force to Remove Safety Guard: Test method for measuring the amount of force required to remove the Safety Guard from the device. (n=20)	FDA Draft Guidance on Injectors	(b)(4) lbf	PASS (b)(4)

Description	References	Acceptance Criteria	Batch Tested / Results
Lock Out and Crush Test Report: Test to verify the ability of the Safety Guard to resist highly compressive forces applied directly and indirectly to it.	FDA Draft Guidance on Injectors	1. Crush (force applied to overall device) \geq (b)(4) lbf 2. Electronic Prompt System voice sequence functions correctly 3. Lock out (force applied to break lock feature- safety guard) \geq (b)(4) lbf	PASS Batch - N/A 1. Volume dispense within acceptance criteria post crushing load. 2. EPS functioned correctly after crushing load. 3. Devices tested in both vertical and horizontal positions. All units passed
Injection Through Material Test Report: Test to investigate the functionality of NAI when injected through various clothing materials. (n=20)	User FMEA	Inject through (b)(4) layers of duck cloth Volume Dispensed: (b)(4) mL	PASS (b)(4)

Description	References	Acceptance Criteria	Batch Tested / Results
Force to Remove Cover Test: Test method for measuring the amount of force required to remove the Outer Case from the device. (n=20)	FDA Draft Guidance on Injectors	> (b) (4) b minimum < (b) (4) b maximum	PASS (b) (4)
Base Activation Force: Verification test method for measuring force required to activate the base and fire the device. Tested utilizing the Release Testing protocol and on the Release Test Fixture. (n=60)		(b) (4) lbf (Release)	PASS (b) (4)

Description	References	Acceptance Criteria	Batch Tested / Results
IEC Testing: Testing for the electronic prompt system component of NAI. All IEC60601 tests need to be performed per applicable ISO11608 sections as well.	ISO11608-1 (Section 11) IEC 60601-1-1 IEC 60601-1-2	Pass/Fail (Meets ESD, EMC, RF and other IEC requirements)	PASS Batch - N/A
Battery Life Test Report: Test to determine the number of cycles that NAI's electronic prompt system can perform. (b) (4)		Electronics Script must function (b) (4) cycles	PASS (b) (4)

Description	References	Acceptance Criteria	Batch Tested / Results
Battery Contact and Life Testing / Label Wear and Adhesion: Test method for life testing for use of the electronic prompt system battery contact/outer case removal. Includes removing and replacing the outer case a minimum of (b)(4) times, verifying the electronic prompt system functionality, and drop testing.		1. No label peeling 2. No wear on label 3. Electronic Prompts function after removal & replacement of outer case (b)(4) cycles + drop testing	Batch - N/A 1. PASS 2. PASS 3. PASS
Sound Level Testing: Test method for determining the sound level of the electronic prompt system. Performed by placing device (b)(4) meters away from microphone and measuring dB level.		Minimum (b)(4) dB measured at a distance of (b)(4) m from front of device	PASS Batch - N/A Avg (b)(4) dB

Description	References	Acceptance Criteria	Batch Tested / Results
Flex Circuit Tear-Through Test: Test to verify that both the safety guard and base tear-through switches that advance the electronic prompts for the electronic prompt system function correctly.		Electronic Prompt System progresses through instructions as each step of activation occurs	PASS Batch - N/A
NAI Interactive System Accelerated Aging Test Report: Test method for applying Accelerated Age Testing of the electronic prompt system during the NAI qualification process.		Post Accelerated Aging the Electronic Prompt System progresses through instructions as each step of activation occurs	PASS Batch - N/A The electronic interactive systems, which were aged from (b)(4) to (b)(4) months, operate consistently and properly.

Description	References	Acceptance Criteria	Batch Tested / Results
<p>Device Accelerated Age Test Plan Report: Full devices placed in chambers to simulate shelf life. (b)(4) per pull point)</p>	<p>ISO 11608, Medical Plastics and Biomaterials, July/August 1998. Pp. 16-23</p>	<p>Base Activation Force: (b)(4)bf (Release) (b)(4)bf (Stability)</p> <p>Vol. Dispensed (b)(4)mL</p> <p>Dispensing Time NMT (b)(4)ec</p> <p>Exposed Needle Length (b)(4)in</p> <p>Needle Retraction Time: Report results</p> <p>Electronic Prompt System Function: Report Results</p>	<p>MA004</p> <p>Accelerated Aging Group\ (55°C Temperature Group) All samples met all release testing acceptance criteria for Activation Force, Volume Dispensed, Dispensing Time, and Exposed Needle Length. The Needle Retraction times were all less than (b)(4)seconds. The Electronic Prompt System functioned as designed for all samples.</p> <p>Control Group (23°C Temperature Group): All control samples met all release testing acceptance criteria for Activation Force, Volume Dispensed, Dispensing Time, and Exposed Needle Length. The Needle Retraction times were all less than (b)(4)seconds. The Electronic Prompt System functioned as designed for all samples.</p> <p>This simulates 36-months of shelf life storage under ambient conditions.</p>

Description	References	Acceptance Criteria	Batch Tested / Results
<p>Gas Cylinder Shelf Life & Leakage Test Protocol: Test to verify the shelf life and potential for leakage of gas cylinders over time.</p>	IEC 60068-2-30	Study PR-585-1374 / PPD 7539-031: Net weight change (b)(4) (equivalent to (b)(4) psi)	(b)(4)
<p>Sterile Barrier Test Report: Test method for determining how well the snap fits the drug cartridge crimp (b)(4)</p> <p>(b)(4) This indicates how well the sterile barrier is performing using a bubble emission test method. (n=53)</p>	ASTM D3078	No formation and release of an air bubble at (b)(4) psi or greater within (b)(4) seconds	<p>PASS</p> <p>Batch - N/A</p> <p>No leaks detected in the cartridge assemblies tested</p>
Description	References	Acceptance Criteria	Batch Tested / Results
<p>Coring Needle Test Report: This testing was completed by Needle Assembly manufacturer using manufacturer's test protocol for anti-coring of the drug/septum end of the needle. (n=30)</p>	ISO 11608-2	<p>Pass/Fail</p> <p>Visual Inspection for the presence of septum fragments. No fragment shall be longer than (b)(4) mm or have an area larger than (b)(4) mm²</p>	<p>PASS</p> <p>Batch-N/A</p> <p>No septum fragments or particulates were found.</p>
<p>Safe Transit, Distribution, and Shipping Testing: Test methods for standard shipping and packaging testing.</p>	ISTA Guidelines ASTM D4169-08	Pass/Fail	PENDING

Description	References	Acceptance Criteria	Batch Tested / Results
Device Biocompatibility Testing (information provided by supplier): This testing includes testing of biocompatibility according to the ISO 10993 standard or other data showing biocompatibility standards are met.	ISO 10993	Pass/Fail	PASS Batch - N/A
Weld Strength Study: Engineering test to verify the top assembly can withstand higher pressures to provide an appropriate safety factor for the weld joints. (n=20)		Force to remove the Top from the Housing must withstand (b) (4) lbs of linear pull force distributed across the perimeter of the Top	PASS (b) (4)

Description	References	Acceptance Criteria	Batch Tested / Results
Altitude Function Test Protocol: Test method to prove that device functions correctly (delivers dose) at upper altitude limits. (n=20)	FDA Draft Guidance on Injectors	From (b) (4) the Volume Dispensed: (b) (4) mL	PASS (b) (4)

Description	References	Acceptance Criteria	Batch Tested / Results
<p>NAI Exposed Needle Length Test Report: Test to verify devices consistently maintain an exposed needle length, which is equivalent to the amount in which the needle would penetrate the skin into the injection site. (n=60)</p>	ISO 11608	Exposed Needle Length (b)(4); in	<p>PASS</p> <p>(b)(4)</p>
<p>Label Adhesion Test: Testing to verify label adheres properly to device housing and outer case. Tested by pulling on and off outer case.</p>		Pass/Fail	<p>PASS</p> <p>Batch – N/A</p>

Description	References	Acceptance Criteria	Batch Tested / Results
<p>Retraction Spring/Piston Aging Testing: Test method to examine the affects of time on the retraction spring and (b)(4) on the piston to ensure proper retraction.</p>	AAMI TIR17:2008	Retraction occurs NMT (b)(4) seconds	PASS
<p>Label Wear Test: Testing to determine durability of outer case and device labels under normal use conditions. Tested by pulling on and off outer case.</p>		Pass/Fail	<p>PASS</p> <p>Batch – N/A</p>
<p>Liquid Ingress Test: Testing to ensure NAI can withstand water droplets per IEC 60529. (IP21)</p>	IEC 60529	<p>(b)(4)</p> <p>Vol. Dispensed (to specification)</p> <p>Electronic Prompt System progresses through instructions as each step of activation occurs</p>	<p>PASS</p> <p>(b)(4)</p> <p>Not repeated</p>

Description	References	Acceptance Criteria	Batch Tested / Results
Dispensing Time Test Verification test method for measuring the time it takes for the drug to be dispensed. Tested utilizing the Release Testing Protocol and on the Release Test Fixture. (n=63)		NMT (b)(4) seconds	PASS (b)(4)
Retraction Occurrence & Visual Inspection: Testing to determine NAI retraction and that, once fired, NAI is free from defects according to ISO 11608-1. (n=64)	ISO 11608-1	Retraction: NMT (b)(4) sec Visual Inspection: Free from Defects	PASS (b)(4) NMT (b)(4) sec for all devices

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

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

Recommendation: No further questions from the CDRH Engineering review perspective. Safety and efficacy has been demonstrated in this device.

Lana Shiu, M.D.

Branch Chief

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

/s/

DIANA L WALKER

02/19/2014

Entered into DARRTS for CDRH Consultant:

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General Hospital Devices Branch, DAGID, ODE, CDRH

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: February 4, 2013

Reviewer: Vicky Borders-Hemphill, Pharm.D
Division of Medication Error Prevention and Analysis

Team Leader: Irene Chan, Pharm.D., BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Evzio (naloxone hydrochloride injection, USP),
0.4 mg/0.4 mL

Application Type/Number: NDA 205787

Applicant: Intelliject

OSE RCM #: 2013-1727

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed labels and labeling for Evzio (naloxone hydrochloride injection, USP), NDA 205787, for areas of vulnerability that could lead to medication errors. The Division of Medication Error and Prevention Analysis (DMEPA) initially reviewed labels and labeling for this product in OSE review 2013-1727, dated December 11, 2013. However, since our previous review, the Applicant has submitted additional labels and labeling that were not previously reviewed by DMEPA.

1.1 PRODUCT INFORMATION

The following product information is provided in the January 22, 2014, proposed insert labeling submission.

- Active Ingredient: naloxone hydrochloride injection, USP
- Indication:
 - [REDACTED] (b) (4)
 - [REDACTED] (b) (4)
- Route of administration: intramuscular or subcutaneous
- Dosage form: injection
- Dose: injection once into the anterolateral aspect (outer) of the thigh, through the clothing if necessary; if the desired degree of counteraction and improvement in respiratory function is not obtained, after 2-3 minutes, another dose may be administered. [REDACTED] (b) (4)
- How Supplied: carton containing two pre-filled, single use naloxone auto-injectors (NAI) and a single NAI trainer; each NAI delivers 0.4 mg naloxone hydrochloride (0.4 mL) and is equipped with an electronic voice prompt system that provides audible instructions for use using voice commands and beeps and visual cues (red/green LED lights)
- Storage: Controlled room temperature 59°F to (b) (4) °F. Temperature excursions permitted between 39°F and 104°F. Do not refrigerate or freeze.
- Sponsor: Intelliject

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) uses the principles of human factors and Failure Mode and Effects Analysis,¹ to identify potential sources of errors with container labels, carton and insert labeling. DMEPA evaluated the following:

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Previously Reviewed Labels and Labeling:

- Revised Container Labels submitted January 2, 2014 (Appendix A)
- Revised Carton Labeling submitted January 2, 2014 (Appendix B)
- Revised Information and Instructions for use leaflets for the device and the trainer submitted January 2, 2014

New Labels and Labeling (not previously reviewed):

- Labeling for Trainer outer case from second manufacturing facility (b)(4) - assembled in different country) submitted January 2, 2014 (Appendix A)
- Carton Labeling for new packaging configuration (b)(4) submitted January 2, 2014 (Appendix B)
- Carton Labeling for Professional sample (“Not for Sale”) submitted January 2, 2014 (Appendix B)
- Package insert submitted January 22, 2014

Additionally, DMEPA compared the revised labels and labeling against our recommendations in OSE Review 2013-1727, dated December 11, 2013, to assess whether the revised labels and labeling address our concerns from a medication error perspective.

3 MEDICATION ERROR RISK ASSESSMENT

Our review of the revised device, trainer, device outer case, and trainer outer case labels and carton labeling determined that the Applicant has implemented most of our previous recommendations, and we find those revisions acceptable. However, we do not agree with the Applicant’s request (b)(4). Where we disagreed with the Applicant’s rationale, we provided responses in section 4.2 below.

Our review of the new labeling for the Trainer outer case from the second manufacturing facility determined that it is identical to the Trainer outer case for the first manufacturing facility (b)(4) other than the manufacturer information. We find it acceptable and have no additional recommendations.

Our review of the carton labeling for the professional sample determined that it is identical to the commercial presentation, except for the “Not for Sale” labeling on the back panel, which we find acceptable.

Our review of the carton labeling for the new (b)(4) determined that the statement (b)(4) as the (b)(4) and recommend the removal of that statement (see section 4.2). However, we find the addition of this packaging presentation reasonable because it provides additional access to training devices if requested by healthcare providers. As presented, the Trainer carton labeling provides adequate differentiation using color and text from the carton labeling containing the two devices with active drug.

However, the proprietary name Evzio on the principal display panel is overly prominent and should be presented in the same font size and type as the word “for” immediately preceding it.

4 CONCLUSIONS AND RECOMMENDATIONS

Our review has determined that additional revisions are necessary to reduce the risk for medication errors. DMEPA recommends the following recommendations are implemented prior to approval of this NDA:

4.1 COMMENTS TO THE DIVISION

A. Package insert submitted January 22, 2014

1. Highlights Section – Dosage and Administration

- i. Delete the text (b) (4)
This information detracts from more important dosage and administration information, contains some information that is redundant, and decreases the readability of this section due to clutter of information.
- ii. To improve readability and show proper sequence of steps to take, revise the sentence that reads (b) (4)
to read “An *initial* dose of 0.4 mg of naloxone hydrochloride...4 kg (9 pounds) or greater.”

2. Full Prescribing Information - Section 2 (Dosage and Administration)

- i. For clarity, we recommend including a subsection specific for administration information and reorganize the contents of this section accordingly by bulleting to identify each key administration instruction. Additionally, we recommend including a cross reference to the full instructions for use.
- ii. The sentence that begins with (b) (4)
appears to be promotional in nature. We defer to OPDP regarding the promotional nature of this statement and whether it is appropriate (b) (4)

3. Full Prescribing Information - Section 3 (Dosage Forms and Strengths)

- i. Add the statement “Each Evzio delivers 0.4 mg naloxone hydrochloride injection (0.4 mL)” since this information is missing.

4.2 COMMENTS TO THE APPLICANT

A. General Comments for all Labels and Labeling

1. We do not agree with your proposal to use (b) (4) (b) (4) on the outer case or carton labeling. Per the Office of New Drug Quality Assessment (ONDQA), the established name should appear as designated in the USP monograph on all labels and labels as “naloxone hydrochloride injection, USP”. (b) (4) Additionally, inconsistent use of an established name throughout labels and labeling may be a source of confusion. Alternatively, we would find it acceptable to use “naloxone HCl injection, USP” (b) (4)
- B. Carton Labeling for (b) (4) packaging configuration
1. Remove the statement (b) (4) as (b) (4). Instead, increase the font of the statement “For Practice Only”.
 2. The proprietary name Evzio on the principal display panel is overly prominent and should be revised so it is the same font size and type as the word “for” immediately preceding it.

If you have further questions or need clarifications, please contact Lisa Skarupa, project manager, at 301-796-2219.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

BRENDA V BORDERS-HEMPHILL
02/04/2014

TODD D BRIDGES on behalf of IRENE Z CHAN
02/04/2014

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 205787

Application Type: New NDA

Name /Dosage Form: EVZIO (naloxone hydrochloride injection USP) autoinjector, 0.4 mg (0.4 mg/0.4 mL)

Applicant: kaleo, Inc.

Receipt Date: December 20, 2013

Goal Date: June 20, 2014

1. Regulatory History and Applicant's Main Proposals

The Sponsor has submitted a new NDA for naloxone hydrochloride autoinjector (NAI), 0.4 mg (0.4 mg/0.4 mL). The Sponsor was granted Fast Track designation during the IND and the NDA has been granted Priority review. This new NDA application is a 505(b)(2) referencing NDA 016636, naloxone hydrochloride injection (NARCAN). Although much of the language has been taken from the reference product, the NARCAN label was not in PLR format, and thus the Sponsor has converted the labeling for NAI into PLR format. Additionally, NAI is a drug-device combination, and thus includes device-specific language and an "Instructions for Use" leaflet.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

Sentences were revised to be consistent with Agency practices concerning the use of (b) (4). For example, (b) (4) was changed to "Administer Evzio according to the printed instructions on its labels or the electronic voice instructions."

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- NO** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *Highlights is almost a full page. This will be discussed with the CDTL and during the labeling meeting.*

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *No line between either.*

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *No white space between DA & DF&S.*

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Indications and usage does not reference sections/subsections.*

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *Drug product name is not in all uppercase and needs to be corrected.*

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Selected Requirements of Prescribing Information

Comment:

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *The Applicant did not include the year. It should be 1971, the year of naloxone approval NDA 16636.*

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

NO

Selected Requirements of Prescribing Information

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *Established pharmacologic class must be added.*

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: *Need to revise the included statement to one of the above*

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- NO** 25. The TOC should be in a two-column format.
***Comment:** It is in single column and needs to be revised to two column.*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment: *References were not in the proper format and not in italics.*

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- NO** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: *Need to check and confirm whether listed AEs are pre- or post-marketing, and add appropriate statements.*

- NO** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *Need to check and confirm whether listed AEs are pre- or post-marketing, and add appropriate statements.*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- NO** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *They included Instructions for Use as a subsection 17.2.*

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

DIANA L WALKER
02/04/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: January 21, 2014

TO: Diana Walker, DAAAP/ODEII/OND/CDER/OMPT. WO-22
Room 3240 Diana.Walker@fda.hhs.gov

Parinda Jani, DAAAP/ODEII/OND/CDER/OMPT. WO-22 Room
3166 Parinda.Jani@fda.hhs.gov

Office of combination products at combination@fda.gov

Juandria Williams, GDMAB/DGMPA/OMPQ/OC/CDER/OMPT.
WO-51 Room 4216 Juandria.Williams@fda.hhs.gov

Through: Carl Fischer, Chief, REGODB/DMQ/OC/CDRH/OMPT. WO-66,
Room 3526

From: M. Isabel Tejero, REGODB/DMQ/OC/CDRH/OMPT. WO-66,
Room 3554

Applicant: Kaléo Pharma Inc. (formerly Intelliject)

111 Virginia St, Suite 300
Richmond, VA 23229
FEI # 3007135538

Application # NDA 205787 (IND 112292)

Product Name: Evzio, a Naloxone Auto-Injector (NIA), containing 0.4 mg of
naloxone hydrochloride injection, USP

Consult
Instructions: Evaluate the application for adequacy under 21 CFR part 820
requirements. Additionally, evaluate the need for inspection under
the Medical Device Regulations of any of the facilities listed in the
application.

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205787. This is a rolling review on a high priority clock (6 months). However, because this will be the first opioid antagonist for use in the community to be approved, its review has been given the highest priority by CDER. This consult is a request for the review of the application for applicable 21 CFR part 820 regulatory requirements, and the evaluation of the compliance status of those facilities subjected to applicable 21 CFR part 820 regulations. The sponsor firm has declared that will be showing compliance with the required good manufacture practices as stated in 21 CFR 4.4(a).

(b) (4)

This is a single dose injector (figure 1) with a dosage of 0.4 mg (0.4 mg/ 0.4 mL) naloxone hydrochloride injection, USP.

(b) (4)

It may be used by laypersons or caregivers in the out-of-hospital, non-healthcare environment.

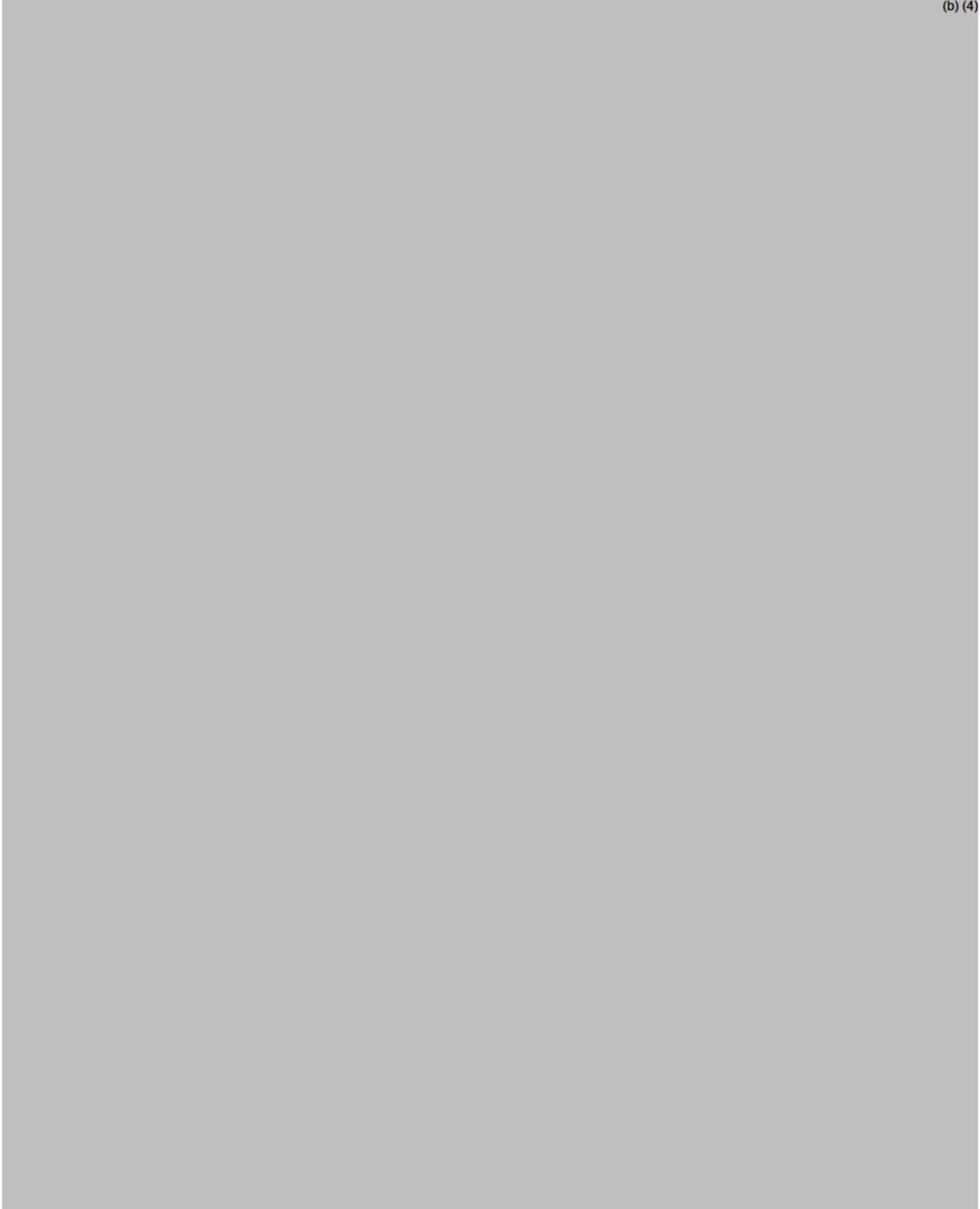


Figure 1
(b) (4)



APPLICATION REVIEW

The application was evaluated for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. The firm provided a master guide specifically for the information covering the Quality System submission requirements. The following documents were reviewed:



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immediately following this page

REGULATORY HISTORY EVALUATION

After reviewing the application, the following facilities were identified as being subject to applicable Medical Device Regulations under 21 CFR part 820:

1. Kaléo Inc.
111 Virginia St, Suite 300
Richmond, VA 23229
FEI # 3007135538

The applicant declared that the firm Kaléo will follow 21 CFR 4.4(a) with regards to show compliance with good manufacturing practices.

An analysis of the firm's inspection history showed that an inspection under the Medical Device regulation was conducted on (b) (4). The inspection was a pre-approval inspection for NDA 201739, epinephrine autoinjector, and was classified NAI.

2. (b) (4)

The applicant declared that the firm (b) (4) will follow 21 CFR 4.4(b)(2) with regards to show compliance with good manufacturing practices.

This firm has been until now a medical device component manufacturer. The Evzio autoinjector is the first finished drug-device combination product this firm will be manufacturing.

An analysis of the firm's inspection history showed that an inspection under the Medical Device regulation was conducted on (b) (4). The inspection covered the manufacturing process for parts of an injector pen, and was classified NAI.

DEFICIENCIES TO BE RELATED TO THE FIRM

(Contact Person)

Kaléo Pharma, Inc.
111 Virginia St, Suite 300
Richmond, VA 23229

The following deficiencies have been identified while doing the desk review of application NDA 205787, in reference to applicable 21 CFR 820 regulations:

Note: these deficiencies pertain exclusively to Kaléo Pharma documents.

1. Following the requirements of 21 CFR820.40, document controls, all procedures and documents provided to show compliance with the regulatory requirements under 21 CFR part 820 should be updated to reflect the firm's name change.
2. Nonconforming product, 21 CFR 820.90 requirements. The following deficiency was found:

a.  (b) (4)

3. Corrective or Preventive Actions (CAPA), 21 CFR 820.100 requirements, the following deficiencies were appreciated:

a.  (b) (4)

b. 

c. 

d. 

CDRH OFFICE OF COMPLIANCE RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of application NDA 205787 and has the following recommendations:

The desk review of the application for compliance with the Medical Device Regulations showed several deficiencies, as related above. Approvability of NDA 205787 under the

Medical Device Regulations should be delayed until the firm has provided an adequate response to the deficiencies found during the desk review (see section “deficiencies to be related to the firm” above).

Additionally, Kaléo, declared to be following the drug regulatory requirements regarding recalls and adverse event reportability. For the purposes of this review, it was assumed that these procedures were already under review by the CDER review team and were not part of the current review.

Furthermore, approvability under the Medical Device Regulations for the application NDA 205787, Evzio naloxone autoinjector, should be delayed until the inspection of the (b) (4) facility located at (b) (4), and with FEI # (b) (4), has been conducted and the site is deemed acceptable.

M. Isabel Tejero del Rio, MD, Ph.D.

Prepared: MITejero: 1/21/2014
Reviewed: CFischer: 1/22/2014

CTS No.: ICC1300133/S001
NDA 205787

Inspectional guidance

Firm to be inspected:



A comprehensive baseline Level 2 inspection is recommended focusing on Management controls, manufacturing including acceptance activities, CAPA and complaint handling.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Dr. M. Isabel Tejero del Rio
CSO
REGODB, DMQ, OC, CDRH, OMPT
Office of Compliance, WO66 RM 3554
Phone: 301-796-5322

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Dr. Carl Fischer
Chief
REGODB, DMQ, OC, CDRH, OMPT
WO-66, Room 3526
Phone: 301-796- 5770

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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/s/

DIANA L WALKER

01/22/2014

Entered into DARRTS for:
Dr. M. Isabel Tejero, REGODB/DMQ/OC/CDRH/OMPT

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205787 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Evzio Established/Proper Name: naloxone hydrochloride injection USP Dosage Form: autoinjector Strengths: 0.4 mg (0.4 mg/0.4 mL)		
Applicant: Kaleo, Inc. Agent for Applicant (if applicable): n/a		
Date of Application: December 20, 2013 Date of Receipt: December 20, 2013 Date clock started after UN: n/a		
PDUFA Goal Date: June 20, 2014	Action Goal Date (if different): Tentatively March 28, 2014.	
Filing Date: February 18, 2014	Date of Filing Meeting: January 10, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) : Type 3/Type 4		
Proposed indication: (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) NDA 016636 <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input checked="" type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 112292				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Sponsor made errors in original 356h in Box 30. They corrected the 356h and submitted the amended form on January 13, 2014.
Are all establishments and their registration numbers listed on the form/attached to the form?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	They were included in a different part of the application. CMC reviewers were contacted to confirm.
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment

<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		<p>A Form 3674 was not submitted with the December 20, 2013, submission.</p> <p>Requested via email and also the Acknowledgement letter. Sponsor submitted prior to Filing meeting.</p>
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Included although this is an electronic submission.</p>
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PeRC date requested and scheduled.
Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	PN was reviewed and found acceptable during the rolling review stage.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted. A PI in PLR format was not submitted with the December 20, 2013, submission. A request was sent via email, requesting submission by January 3, 2014. The Sponsor submitted a PI in	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	<input checked="" type="checkbox"/> Package Insert (PI)	<input type="checkbox"/> Patient Package Insert (PPI)	<input checked="" type="checkbox"/> Instructions for Use (IFU)	<input type="checkbox"/> Medication Guide (MedGuide)
	<input type="checkbox"/> Carton labels			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

PLR format prior to the filing meeting	<input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		SPL was requested via email and in the Acknowledgement letter.
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		A PI in PLR format was not submitted with the December 20, 2013, submission. A request was sent via email, requesting submission by January 3, 2014. The Sponsor submitted a PI in PLR format prior to the filing meeting
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	To be consulted.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	DMEPA consulted reviewed PN, C&C, IFU, voice script, and HF study.
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDRH consulted for: Devices Human Factors Compliance
<i>If yes, specify consult(s) and date(s) sent:</i>				OSE/DEPI consulted. Pediatrics consulted.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		There was a PIND meeting August 16, 2011.
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): June 4, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 10, 2014

NDA #: 205787

PROPRIETARY NAME: Evzio

ESTABLISHED/PROPER NAME: naloxone hydrochloride injection USP

DOSAGE FORM/STRENGTH: autoinjector, 0.4 mg (0.4 mg/0.4 mL)

APPLICANT: Kaleo, Inc.

PROPOSED INDICATION: [REDACTED] (b) (4)

BACKGROUND: The Sponsor was granted Fast Track Designation, as well as a rolling review and Priority review status. The first submission was received July 19, 2013, and the final submission of the rolling review was received on December 20, 2013, triggering the 6-month PDUFA clock.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diana Walker	Y
	CPMS/TL:	Parinda Jani	Y
Cross-Discipline Team Leader (CDTL)	Joshua Lloyd		Y
Clinical	Reviewer:	Steven Galati	Y
	TL:	Joshua Lloyd	Y

Clinical Pharmacology	Reviewer:	Wei Qiu	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	n/a	n/a
	TL:	Janice Derr	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carlic Huynh	Y
	TL:	Daniel Mellon	Y
Product Quality (CMC)	Reviewer:	Ying Wang	N
	TL:	Julia Pinto	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	Y
	TL:	Stephen Langille	N
Facility Review/Inspection	Reviewer:	Juandria Williams (CMC) Isabel Tejero (CDRH)	Y Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Vicky Borders-Hemphill	N
	TL:	Irene Chan Jim Schlick (substituting)	N Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Devices (CDRH)	Reviewer:	Lana Shiu	Y
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:	William Taylor	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Chih-Ying Chen (Natacha) – DEPI reviewer Cynthia Kornegay – DEPI YL		
Other attendees	Lisa Skarupa (OSE RPM) Bindi Nikhar – Office Combination Products (OCP) Sharon Hertz – Deputy Director, DAAAP Bob Rappaport – Director, DAAAP		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO BA/BE study to the generic RLD
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: no comments</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
Comments:	

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: No clinical studies performed by Applicant. See below for Clinical Pharmacology BA/BE inspections.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p>If no, for an NME NDA or original BLA, include the reason. For example:</p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined. Dr. Hertz is confirming with other management. Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES – BE study. Consult request already sent with assistance of the

	clinical pharmacology review team. <input type="checkbox"/> NO
BIOSTATISTICS Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO Comments: this will be done by ONDQA	
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO Comments: Fileable, but have comments for the 74-day letter.	<input type="checkbox"/> Not Applicable

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: ONDQA Compliance and CDRH Compliance are working together on this application and inspections.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: N/A at this point, will be done during review.</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: TBD, will be either Dr. Hertz or Dr. Rappaport

Date of Mid-Cycle Meeting: March 19, 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: This review will be expedited and we will try to take an early action if possible (tentatively the end of March, 2014), therefore milestone meetings will be revised. Mid-cycle will be March 19, 2014.

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): Clinical CMC Microbiology</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input checked="" type="checkbox"/>	Other: Schedule PeRC for late February or early March. Complete and submit b2 assessment as soon as possible for early action (due 2 months prior to action date). Prepare consult for OPDP.

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/s/

DIANA L WALKER
01/13/2014

PARINDA JANI
01/13/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: December 11, 2013

Reviewer: Vicky Borders-Hemphill, Pharm.D.
Division of Medication Error Prevention and Analysis

Acting Team Leader: Morgan Walker, Pharm.D.
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, Pharm.D., MPH
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Naloxone Hydrochloride Injection, USP, 0.4 mg/0.4 mL Auto-
Injector

Application Type/Number: NDA 205787

Applicant: Intelliject

OSE RCM #: 2013-1727

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed labels and labeling for Evzio (naloxone hydrochloride injection, USP), NDA 205787, for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the July 17, 2013, proprietary name submission.

- Active Ingredient: naloxone hydrochloride injection, USP
- Indication:
 - (b) (4)
 - (b) (4)
- Route of administration: intramuscular or subcutaneous
- Dosage form: injection
- Dose: injection once into the anterolateral aspect (outer) of the thigh, through the clothing if necessary; if the desired degree of counteraction and improvement in respiratory function is not obtained, after 2-3 minutes, another dose may be administered.
- How Supplied: carton containing two pre-filled, single use naloxone auto-injectors (NAI) and a single NAI trainer; each NAI delivers 0.4 mg naloxone hydrochloride (0.4 mL) and is equipped with an electronic voice prompt system that provides audible instructions for use using voice commands and beeps and visual cues (red/green LED lights)
- Storage: Controlled room temperature 59°F to (b) (4)°F. Temperature excursions permitted between 39°F and 104°F. (b) (4)
- Sponsor: Intelliject

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) uses the principles of human factors and Failure Mode and Effects Analysis,¹ to identify potential sources of errors with container labels, carton and insert labeling. DMEPA evaluated the following:

- Container Labels submitted July 19, 2013 (Appendix A)
- Carton Labeling submitted July 19, 2013 (Appendix B)
- Information and Instructions for use leaflets for the device and the trainer submitted July 19, 2013

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

BRENDA V BORDERS-HEMPHILL
12/12/2013

IRENE Z CHAN on behalf of KELLIE A TAYLOR
12/12/2013