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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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2/11/2014

Product: Evzio or Naloxone auto-injector (NAI)

Indication:  (b) (4)

Applicant: Kaleo, Inc.

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

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1 Executive Summary

1.1 Introduction

Naloxone hydrochloride was first approved by the FDA in 1971 for intravenous, intramuscular, and subcutaneous administration. There is extensive clinical experience with naloxone. The Applicant, Kaleo, Inc., is submitting this NDA for a novel naloxone hydrochloride single-use auto-injector that incorporates both audio and visual cues to guide the patient and caregiver on how to use the auto-injector in the case of an emergency. The drug product was developed with the intention for it to be used by laypersons or caregivers in the out-of-hospital, non-healthcare environment.

1.2 Brief Discussion of Nonclinical Findings

The Applicant did not submit any nonclinical studies to support this marketing NDA. The naloxone drug formulation does not contain any novel excipients. The specifications as proposed for drug substance impurities and drug product degradants meet ICH Q3A(R2) and Q3B(R2) qualification thresholds and are acceptable. An extractables study and a leachables assessment in the ongoing stability studies were done to justify the safety of the container closure system and the levels of leachables found as a result of these studies do not represent a safety concern. This is a 505(b)(2) application and the Applicant is relying upon the Agency's previous finding of safety and efficacy for Endo's Narcan (NDA 16636). As the Narcan NDA has been withdrawn (not for reasons of safety or efficacy), the relative bioavailability study compared the product to the generic drug product marketed by International Medication Systems (ANDA 72076).

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, the drug product, naloxone autoinjector, may be approved with the recommended labeling changes and without any post-marketing nonclinical studies.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

The following changes to the Applicant's proposed labeling are illustrated in the table below:

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
(Highlights) INDICATIONS AND USAGE (b) (4)	(Highlights) INDICATIONS AND USAGE Evzio, an opioid antagonist , is indicated for . . .	The established pharmacological class was added.
USE IN SPECIFIC POPULATIONS (b) (4)	USE IN SPECIFIC POPULATIONS (b) (4)	For a Pregnancy Category B drug, the Maternal Health team generally recommends that nothing be included in the highlights.
8.1 Pregnancy Teratogenic Effects Pregnancy Category B (b) (4)	8.1 Pregnancy Teratogenic Effects Pregnancy Category B (b) (4)	The Narcan label contains a Pregnancy Category C. Several generic drug products are a Pregnancy Category B. The Narcan pregnancy category was apparently changed in 2001 to a C. This may have been inadvertent. The PT, MO, and RPM reviews of that supplement do not recommend a change. The AE letter, suggests changes to the "Use in Pregnancy-Teratogenic Effects Pregnancy Category C" subsection, which may have been interpreted to be a change in the category.
There are, (b) (4), no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone hydrochloride should be used during pregnancy only if clearly needed.	There are (b) (4) no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone hydrochloride should be used during pregnancy only if clearly needed. Teratology studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m ²), demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.	As per the Maternal Health labeling initiative, human data is now stated first. The referenced Narcan labeling was updated in 2001; however, it appears as though the generic labels were not all updated accordingly. The proposed text is consistent with some of the generic labels and the revisions proposed are consistent with the updated

		Narcan label.
<p>10. OVERDOSAGE There is no clinical experience with naloxone hydrochloride overdose in humans.</p> <p>(b) (4)</p>	<p>10. OVERDOSAGE There is no clinical experience with naloxone hydrochloride overdose in humans.</p> <p>(b) (4)</p>	<p>(b) (4)</p> <p>(b) (4) We defer to the clinical team to determine what human data should be included in this section.</p>
<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>(b) (4)</p>	<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>(b) (4)</p>	<p>These sections were divided with subheaders for clarity.</p>
	<p>Carcinogenesis. Long-term animal studies to evaluate the carcinogenic potential of naloxone hydrochloride have not been completed.</p> <p>Mutagenesis. Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.</p> <p>Impairment of Fertility.</p>	<p>The Narcan labeling was updated in 2001 to include genetic toxicology data. These changes were not apparently incorporated into all of the generic drug product labeling. The proposed labeling is consistent with some of the generic drug products labeling.</p>

	<p>Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no adverse effect of naloxone hydrochloride on fertility.</p>	<p>The referenced Narcan labeling was updated in 2001 to include exposure margins. We recommend modifying the text to address only the fertility endpoints, consistent with the subsection header.</p>
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2 Drug Information

2.1 Drug

CAS Registry Number
51481-60-8

Generic Name
Naloxone hydrochloride dihydrate

Code Name
N/A

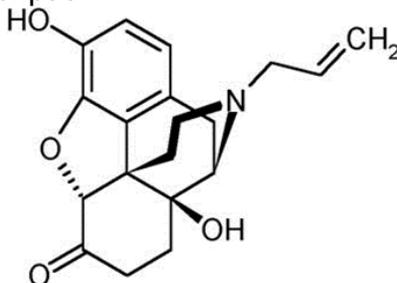
Chemical Name
17-Allyl-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate

Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5 α) dihydrate

(1S,5R,13R,17S)- 10,17-dihydroxy- 4-(prop-2-en-1-yl)- 12-oxa- 4-azapentacyclo [9.6.1.01,13.05,17.07,18] octadeca- 7(18),8,10-trien- 14-one

Molecular Formula/Molecular Weight
 $\text{C}_{19}\text{H}_{21}\text{NO}_4 \cdot \text{HCl} \cdot 2\text{H}_2\text{O}$ / (b) (4) g/mol

Structure or Biochemical Description



Pharmacologic Class
Opioid receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND#	Drug	Status	Division	Indication	Status Date	Sponsor
112292	Naloxone autoinjector (NAI)	Active	DAAAP	Opioid overdose	12/16/2012	Intell ject VA Inc. (now Kalao)

NDA	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
16636	Narcan (Naloxone HCl) Inj	DAAAP	0.2, 0.4, and 1 mg/mL (Injection)	Withdrawn	August 20, 2010	Opioid Dependence	Endo Pharmaceuticals, Inc.

ANDA	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
72076	Naloxone HCl	OGD	1 mg/mL (Injection)	Approved	March 24, 1988	Opioid Dependence	International Medication System

DMF#	Subject of DMF	Holder	Submit Date	Reviewer's Comment
		(b) (4)	October 31, 2007	DMF was deemed adequate in a CMC review dated January 28, 2011).
			April 24, 2007	DMF was deemed adequate in a CMC review dated September 19, 2012.
			September 11, 1995	This MF covers the (b) (4). DMF was deemed adequate in a CMC review dated January 7, 2011.
			January 25, 1972	DMF was deemed adequate in a CMC review dated October 3, 2012.

2.3 Drug Formulation

The following table illustrates the drug formulation for the naloxone auto-injector (from the Applicant's submission):

Table 3.2.P.1-1. NAI Drug Product Constituent Ingredients

Component	Function	Amount	Specification
Naloxone HCl, Anhydrous ¹	Active	1 mg/mL	USP, EP
Sodium Chloride	(b) (4)	(b) (4) mg/mL	USP/NF, EP
Hydrochloric Acid		qs ad to pH 3.0 - 4.5	USP/NF, EP
Water for Injection		qs ad (b) (4) mL	USP/NF, EP
¹ Equivalent to 1.1 mg/ml naloxone HCl dihydrate			

As shown in the table above, the formulation is made up of sodium chloride, water, and hydrochloric acid for pH adjustment. The concentration of the naloxone drug product is 1 mg/mL; however, the volume is 0.4 mL. Thus, the drug product is 0.4 mg of naloxone formulated in 0.4 mL of solution.

The drug product will be packaged as a set of 2 naloxone auto-injector (b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation.

According to the referenced product label for naloxone HCl (Endo Pharmaceuticals, October, 2001), multiple doses of 0.4 mg may be given if improvement in respiratory function is not obtained. The label notes that (b) (4)

Sodium chloride is present in various FDA-approved parenteral products as searched in the DPRF with adequate coverage for dose and duration of use as compared to this drug product. Thus, the amount of sodium chloride in this drug formulation does not represent a safety concern.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance:

The specification for the drug substance is illustrated in the following table (note the drug substance is supplied as naloxone hydrochloride dehydrate) that is adapted from the Applicant's submission:

Test	Method	Specification
(b) (4)	Naloxone HCl USP monograph	(b) (4) % maximum
Related substances (b) (4)	EP<2.2.29>	% max
		% max
Unknown impurities (each)		% max
Total related substances		% max
Assay	In house method (b) (4) #940907	(b) (4)
Naloxone		(b) (4) % w/w max
(b) (4)		(b) (4) % w/w max
		(b) (4) % w/w max
		(b) (4) % w/w max
Unknown (each)		(b) (4) % w/w max
Total related substances		(b) (4) % w/w max
Identification (UV) (b) (4)		(b) (4)
(b) (4)	In house method (b) (4) #777	(b) (4) % w/w max

The table above lists the European Pharmacopeia (EP) specifications as well as the in-house specifications that will be employed for this drug product in order to comply with ICH guidelines. For a drug with a maximum daily dose of approximately 10 mg, the proposed in-house drug substance specifications of NMT (b) (4) % for each impurity would result in (b) (4) mcg for each impurity, which meet the ICH Q3A(R2) qualification threshold. According to the CMC reviewer, the drug substance will be tested using both methods (the reader is referred to the CMC review). Thus, the proposed drug substance specifications (for in-house method (b) (4) #940907) are acceptable.

It is noted that current levels of (b) (4) do not exceed ICH Q3A(R2) qualification thresholds of NMT (b) (4) % or (b) (4) mg/day intake (whichever is lower) for drug products with a maximum daily dose of ≤ 2 g/day. However, (b) (4) contains an (b) (4) structural alert for mutagenicity. The Agency is aware of data that suggests that this compound has been reported to be negative for mutagenicity in the Ames assay but has tested positive for clastogenicity in the in vitro chromosome aberration assay. When first identified as a potential genotoxic impurity in 2002, the Division required this impurity to be controlled at NMT (b) (4) %. In the 2008 FDA draft guidance titled “Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches”, the Agency proposed that all genotoxic impurities be reduced to NMT (b) (4) mcg/day by the time of NDA approval. For a drug product with a maximum daily dose of approximately 10 mg/day, the proposed drug substance specification of NMT (b) (4) % would result in (b) (4) mcg of (b) (4). Thus, the proposed specification is acceptable.

The container closure system for the bulk drug substance is a (b) (4). For quantities between (b) (4) kg, a (b) (4). There are no safety concerns with the container closure system for the bulk drug substance as this container closure system has been used in many drug substances (the reader is referred to the CMC review).

Drug Product:

The following table illustrates the drug product specifications and batch analysis (adapted from the Applicant’s submission):

Test	Analytical Procedure	Acceptance Criterion	NAI Release	Drug Constituent Component and NAI Stability/Shelf Life
Appearance	Visual	Clear, colorless solution in a glass cartridge with a gray plunger and crimp cap.	X ^a	X
pH	USP	3.0 – 4.5	X ^a	X
Osmolality	USP	(b) (4) mOsm/kg	X ^c	
Identification	Section 3.2.P.5.2.1 (ATM-8v3)	Matches reference standard retention time.	X ^a	
Assay	Section 3.2.P.5.2.1 (ATM-8v3)	(b) (4) % LC	X ^a	X
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3)	(b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT Single Unspecified: NMT Total Impurities: NMT	X ^a	
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3)	(b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT Single Unspecified: NMT Total Impurities: NMT		X

a = Results taken from testing conducted on Drug Cartridge Assembly.
 c = Results taken from Drug Constituent release testing at Vetter (Section 3.2.P.3.4).

As per the referenced product labeling, the maximum daily dose is 10 mg. That being said, this particular drug product is intended to be used in the outpatient setting and will likely only be dispensed as 2 devices per package. That would result in a typical total drug delivery of 0.8 mg per day (in 0.8 mL). The ICH Q3B(R2) qualification thresholds are based on a maximum daily dose of less than 10 mg or between 10 mg to 100 mg. As shown in the table above, the levels of degradants at release meet the ICH Q3B(R2) qualification threshold of NMT (b) (4) mcg (whichever is lower) for drug products with a maximum daily dose of < 10 mg/day. For a worst-case maximum daily dose of approximately 10 mg of naloxone, the proposed specification at release of NMT (b) (4) % for each degradant would result in (b) (4) mcg for each degradant, which meet the ICH Q3B(R2) qualification threshold. The levels of degradants upon stability meet the ICH

Q3B(R2) qualification threshold of NMT (b) (4) mcg (whichever is lower) for drug products with a maximum daily dose of < 10 mg/day. For a maximum daily dose of approximately 10 mg of naloxone, the proposed specification at release of NMT (b) (4) % for each degradant would result in (b) (4) mcg for each degradant, which meet the ICH Q3B(R2) qualification threshold. Moreover, the specification of 2,2'-bisnaloxone has been lowered to NMT (b) (4) % both at release and upon stability as per the preIND meeting minutes (the reader is referred to the meeting minutes from September 1, 2011 under IND 112,292). It is noted that the drug substance impurity (b) (4) was not included in the drug product specification as a degradant because this drug substance impurity is not expected to be a drug product degradant. Thus, the proposed drug product specifications are acceptable.

Container Closure System:

The container closure system for the drug product is illustrated in the following table (from the Applicant's submission):

Table 3.2.P.7-1: Container Closure Components

Component	Description	DMF ^a	Supplier
(b) (4)			

^a Letters of authorization to reference the respective DMFs are provided in Section 1.4.1.

As shown in the table above, the container closure system is comprised of a glass cartridge (DMF (b) (4)), crimp cap with rubber septum (DMF (b) (4)), and plunger (DMF (b) (4)). These are the only components that come in contact with the drug product solution during storage. As noted during the preIND meeting, extractables and leachables testing is required at the NDA submission due to the rubber cap and plunger, unless otherwise justified. The rubber septum in the cap and plunger are made of (b) (4) rubber (b) (4) (b) (4) gray. The Applicant has submitted an extractables evaluation of the (b) (4) Gray Piston and Seal using isopropanol and placebo as well as an evaluation of the leachables upon stability for up to 12 months.

For the extraction studies, duplicate samples of 50 cm² (equating to 21 whole plungers and 51 whole seals) were placed in separate extraction flasks for each extraction

solvent. The extraction solvent used was 50 mL of isopropanol and placebo under the appropriate conditions for an extraction study. To detect non-volatile organic extractables, LC/MS analysis was used. To detect semi-volatile organic extractables, GC/MS analysis was used. Metals were detected using inductively-coupled plasma (ICP) analysis.

The extracts were then examined to determine if there was a need for further risk assessment evaluation. As per Division policy, risk assessment would be required if the levels of the extracts exceed the toxicological threshold of concern of (b) (4) mcg/day as per the safety qualification threshold in orally inhaled and nasal drug products from the Product Quality Research Institute (PQRI) (Ball et al. 2007).

The following table illustrates the identified non-volatile organic extractables in the (b) (4) Gray Piston and the (b) (4) Gray Lined Seal using isopropanol and detected by LC/MS analytical techniques (adapted from the Sponsor’s submission):

RT (min)	Identity (wavelength in nm)	(b) (4) Gray Piston				(b) (4) Gray Lined Seal			
		Replicate 1		Replicate 2		Replicate 1		Replicate 2	
		Sample ^a (mcg/cm ²)	MDD ^b (mcg/day)	Sample ^a (mcg/cm ²)	MDD ^b (mcg/day)	Sample ^a (mcg/cm ²)	MDD ^b (mcg/day)	Sample ^a (mcg/cm ²)	MDD ^b (mcg/day)
(b) (4)									

a = levels of each extractable was calculated based on the 50 cm total sample of plungers and seals per 50 mL of solvent.

b = for the purposes of extractables risk assessment, the maximum daily dose (MDD) for this drug product is 2 doses as two naloxone auto-injectors will be packaged together and prescribed to patients.

ND = not detected

N/A = not applicable

As shown in the table above, a number of non-volatile organic were identified by LC/MS and their levels were above the toxicological threshold of concern of (b) (4) mcg/day. These extractables were extracted from the pistons and seals using isopropanol. No extractables were detected using placebo.

The following table illustrates the identified semi-volatile organic extractables in the (b) (4) Gray Piston and the (b) (4) Gray Lined Seal using isopropanol and detected by GC/MS analytical techniques (adapted from the Sponsor’s submission):

RT, min	Identity	(b) (4) Gray Piston				(b) (4) Gray Lined Seal			
		Replicate 1		Replicate 2		Replicate 1		Replicate 2	
		Sample ^a (mcg/cm ²)	MDD ^b (mcg/day)						
(b) (4)									

a = levels of each extractable was calculated based on the 50 cm² total sample of plungers and seals per 50 mL of solvent.

b = for the purposes of extractables risk assessment, the maximum daily dose (MDD) for this drug product is 2 doses as two naloxone auto-injectors will be packaged together and prescribed to patients.

As shown in the table above, a number of semi-volatile organic extractables were identified by GC/MS and their levels were above the toxicological threshold of concern of (b) (4) mcg/day. These extractables were extracted from the pistons and seals using isopropanol. No extractables were detected using placebo.

The following table illustrates the metals detected using placebo (adapted from the Sponsor's submission):

Analyte	(b) (4) Gray Piston				(b) (4) Gray Lined Seal				Placebo Blank (mcg/cm ²)
	Replicate 1		Replicate 2		Replicate 1		Replicate 2		
	Sample ^a (mcg/cm ²)	MDD ^b (mcg/day)	Sample ^a (mcg/cm ²)	MDD ^b (mcg/day)	Sample ^a (mcg/cm ²)	MDD ^b (mcg/day)	Sample ^a (mcg/cm ²)	MDD ^b (mcg/day)	
(b) (4)									

a = levels of each extractable was calculated based on the 50 cm² total sample of plungers and seals per 50 mL of solvent.

b = for the purposes of extractables risk assessment, the maximum daily dose (MDD) for this drug product is 2 doses as two naloxone auto-injectors will be packaged together and prescribed to patients.

As shown in the table above, the levels of the metals (b) (4) that were found in the piston and seal during extraction with placebo when the considering the MDD were below the toxicological threshold of concern of 5 mcg/day.

In the extraction studies of the (b) (4) Gray Piston and the (b) (4) Gray Lined Seal using isopropanol, (b) (4), and several unknowns were identified as extracts using LC/MS analysis exceed the toxicological threshold of concern at (b) (4) mcg/day. However, no organic extractables were identified in the extraction study using placebo.

In the extraction studies of the (b) (4) Gray Piston and the (b) (4) Gray Lined Seal using isopropanol, (b) (4) were identified as extracts using GC/MS analysis exceed the toxicological threshold of concern at (b) (4) mcg/day. However, no organic extractables were identified in the extraction study using placebo.

(b) (4), (b) (4), (b) (4), and (b) (4) were the metals identified in the placebo extracts in the extraction studies of the (b) (4) Gray Piston and the (b) (4) Gray Lined Seal. The metals identified were below the toxicological threshold of concern of 5 mcg/day. As per the draft ICH Q3D guidance, and current Agency policy, metals such as (b) (4), if found, have low inherent toxicity and do not require a risk assessment.

Based on the extraction study, the extractables identified aided in the identity of substances to test for in the leachables assessment. (b) (4)

(b) (4). At the time of this review stability data up to 12 months was available. The leachables were detected via LC/MS and GC/MS while metals were detected via ICP analytical methods.

The following table illustrates the leachables assessment in the ongoing stability studies (adapted from the Applicant's submission):

Table 3.2.P.8.3-12. Physicochemical and Microbiological Stability Data for Registration Batch Stored at Long-Term Condition (continued)

Product Components:	API (Naloxone HCl)	Cartridge (b) (4) mL Fill	Auto-Injector	Product:	NAI	
Lot:	1002000897	INLG02	NA	Storage Condition:	25 ± 2°C/60 ± 5% RH	
Manufacturer:	(b) (4)	(b) (4)	NA	Initiation Date:	08/23/2012	
Manufacture Date:	March 2010	07/21/2012	NA	Testing Facility:	(b) (4)	
Container/Closure:	Cartridge (b) (4) USP	Plunger (b) (4) rubber plunger		Crimp Seal	(b) (4) lined crimp seal	
Description:	(b) (4) glass	(b) (4)				
Supplier:	(b) (4)				West	
				Time Point		
Test	Specifications	Initial	1 Month	3 Months	6 Months	
Particulate Matter	NMT (b) (4) ≥ (b) (4) μm and (b) (4) μm and per container (b) (4)	ND (b) (4) μm: (b) (4) μm:	NS	NS	ND (b) (4) μm: (b) (4) μm:	
Bacterial Endotoxin	NMT (b) (4) EU/mg of Naloxone HCl	< (b) (4) EU/mg			< (b) (4) EU/mg	
Sterility	Conforms	Complies			Complies	
Leachables	Report results	No packaging extractable peaks observed during LCMS and GCMS analyses. Al (< (b) (4) μg/mL) by ICP.			No packaging extractable peaks observed during LCMS and GCMS analyses. (b) (4) μg/mL) by ICP.	
				Time Point		
Test	Specifications	9 Months	12 Months	18 Months	24 Months	36 Months
Particulate Matter	NMT (b) (4) ≥ (b) (4) μm and (b) (4) μm and per container (b) (4)	NS	ND (b) (4) μm: (b) (4) μm:	NS		
Bacterial Endotoxin	NMT (b) (4) EU/mg of Naloxone HCl		(b) (4) EU/mg			
Sterility	Conforms		Complies			
Leachables	Report results		No packaging extractable peaks observed during LCMS and GCMS analyses. (b) (< (b) (4) μg/mL) by ICP.			

LOQ – Limit of quantitation.
 ND – Not detected.
 NMT – Not more than.
 NS – Not scheduled.

As shown in the table above, there were no leachables identified in up to 12 months of stability data. (b) (4) was identified and quantified at the initial and 6 months timepoint and (b) (4) at the 12 months timepoint. At the MDD of 2 auto-injectors (0.8 mL), this would result in (b) (4) of (b) (4) and (b) (4) of (b) (4). The levels of (b) (4) and (b) (4) at the MDD of this drug product would be below the toxicological threshold of concern of 5 mcg/day.

As there were no organic extractables identified in the extraction studies using placebo, the metals identified in the extraction studies using placebo being under the toxicological threshold of concern of (b) (4) mcg/day, and only metals at levels below the toxicological threshold of concern were identified and quantified in the leachables assessment in the stability studies at up to 12 months, there do not appear to be any safety concerns with the container closure system.

2.6 Proposed Clinical Population and Dosing Regimen

(b) (4)
The NAI drug product was developed with the intention for it to be used by laypersons or caregivers in the out-of-hospital, non-healthcare environment.

NAI is formulated as a 0.4 mg/0.4 mL single-use naloxone hydrochloride injection USP solution, for intramuscular or subcutaneous administration, in a pre-filled auto-injector. It will be dispensed in a package of two devices.

The proposed initial dose of 0.4 mg of naloxone hydrochloride may be administered intramuscularly or subcutaneously. As per the proposed labeling, if the desired degree of counteraction and improvement in respiratory functions is not obtained, after 2 or 3 minutes, another Evzio dose may be administered. The maximum daily dose of naloxone hydrochloride, as per the Narcan labeling, is 10 mg; however, in the intended out of hospital use setting, this dose is not likely to be available.

There is no pediatric section in the Narcan labeling. As per the proposed product labeling, “(b) (4)
”

2.7 Regulatory Background

Naloxone HCl was originally approved in since 1971 and first marketed by Endo as Narcan® injection (NDA 016636). Naloxone HCl injection has then subsequently become available as a generic drug with various concentrations manufactured by International Medication Systems, Ltd. and Hospira, Inc. (ANDAs 70172, 70254, 70256, 70257, 70639, and 72076).

Regulatory meetings were held under IND 112292 with the Sponsor, Intelliject, Inc.

There was a preIND meeting with the Applicant on August 16, 2011 (seeing meeting minutes from September 1, 2011). Questions 6a, 6b, and 14 have nonclinical implications and are reproduced below:

Question 6a. Does the Agency agree that Intelliject can reference (through a LOA) the chemistry, manufacturing, and control information in the API active DMF (conforming to the requirements of the FDA Guideline for DMF, September 1989) to provide the drug substance information for the NAI NDA?

FDA Response:

We agree that you can reference the DMF.

Discussion:

There was no further discussion on this point.

Question 6b. Acknowledging that final specification for the drug substance will be set during NDA review; does the Agency agree that the currently proposed specifications appear generally acceptable?

FDA Response:

We agree; your proposed specifications appear reasonable for IND submission. At the time of the NDA submission, specifications must comply with ICH Q3A, Q3B, and the FDA draft guidance on structural alerts.

For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R2), ICHQ3B(R2)). Adequate qualification must include:

- **Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
- **Repeat dose toxicology of appropriate duration to support the proposed indication.**

In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.

NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the ICH qualification thresholds.

Discussion:

There was no further discussion on this point.

Question 14. Does the Agency agree that Intelliject, Inc. can rely on the Agency's previous findings of safety and efficacy for naloxone HCl and therefore no

additional nonclinical studies and no literature summaries are required to support marketing approval of NAI?

FDA Response:

You may rely upon the Agency's previous finding of safety for an FDA-approved NDA without conducting any additional toxicology studies for naloxone drug substance. However, given the initial approval date of Narcan (1971), your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the public domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

Additional data may be needed to support the safety of the drug product formulation. The following additional comments pertain to your NDA submission:

We note that you intend to conduct both extractable testing and leachable assessments of the primary container closure system over 6 month stability. The NDA submission must contain complete and definitive safety information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled *Container Closure Systems for Packaging Human Drugs and Biologics*. The evaluation of extractables and leachables from the drug container closure system must include specific assessments for residual monomers, solvents, polymerizers, etc. Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents *Container Closure Systems for Packaging Human Drugs and Biologics* and *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*. Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at [http://www.pqri.org/pdfs/LE Recommendations to FDA 09-29-06.pdf](http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf).

We note that you are currently proposing a drug product specification for 2,2-bisnaloxone of NMT $\frac{(b)}{(4)}\%$. This exceeds the current ICH Q3B(R2) qualification threshold of NMT $\frac{(b)}{(4)}\%$ and must be adequately justified for safety. See response to question 6b regarding the nonclinical requirements for impurity/degradant qualification.

Discussion:

There was no further discussion on this point.

The IND was submitted on November 16, 2012 and the proposed clinical study was allowed to proceed on December 16, 2012.

A preNDA meeting was held with the Applicant on June 4, 2013 (see meeting minutes from June 26, 2013). There were no nonclinical questions presented at the preNDA meeting.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical toxicology studies were submitted in this NDA. As requested, the Sponsor 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 to determine if they contained adequate data to further inform product labeling and safety.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

There were no previous reviews referenced.

4 Pharmacology

4.1 Primary Pharmacology

There were no primary pharmacology studies with naloxone submitted in this NDA.

Naloxone is a nonselective opioid receptor antagonist and binds with high affinity to mu, delta, and kappa opioid receptors. Wang and colleagues report that naloxone inhibited [³H]diprenorphine binding to cloned human mu-opioid receptors, mouse delta-opioid receptors, and human kappa opioid receptors with Ki values of 7, 8, and 4 nM, respectively and display no agonist activity in vitro (Wang, et al., 2007).

Administration of naloxone blocks pharmacological effects of exogenous opioid agonists. As such, naloxone administration to an individual who has been chronically using opioids will elicit classical opioid withdrawal symptoms, including reversal of respiratory depression and sedation. Depending on the amount of naloxone given and the opioid tolerance, naloxone administration may also be associated with rebound

release of catecholamines resulting in hypertension, tachycardia and ventricular arrhythmias (Gutstein and Akil, 2002). Acute withdrawal symptoms will likely include pain, hypertension, sweating, agitation, and irritability.

High doses of naloxone are also able to block the effects of endogenous opioid tone the body. As endogenous opioid tone is generally low in healthy individuals, most of the effects are not believed to have clinical significance. However, naloxone may result in mild dysphoria. As endogenous opioids also regulate pituitary secretion, naloxone can result in increased gonadotropin-releasing hormone and corticotrophin-releasing factor resulting in elevations of plasma luteinizing hormone, follicle stimulating hormone, and ACTH. Opioid antagonists may increase prolactin secretion in women and augment the stress or exercise-induced cortisol and catecholamine release (Gutstein and Akil, 2002).

As per the warnings and precautions section of naloxone labeling, underlying cardiovascular disease may be at greater risk due to the potential for catecholamine release in opioid tolerant individuals. In addition, naloxone may augment seizures in patients with a history of seizures.

4.2 Secondary Pharmacology

There were no secondary pharmacology studies with naloxone submitted in this NDA.

4.3 Safety Pharmacology

There were no new safety pharmacology studies with naloxone submitted in this NDA. The Sponsor's literature review also did not identify any safety pharmacology issues that impact labeling.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

There were no new PK/ADME studies with naloxone submitted in this NDA.

Naloxone is rapidly metabolized in the liver; therefore, the drug is not very effective via oral route of administration unless very high doses are given (1000 to 2500 mg). Oral bioavailability has been reported to be < 1%. The major metabolite is naloxone-3-glucuronide which is excreted in the urine (Gutstein and Akil, 2002).

The plasma half-life ranges from 30 to 90 minutes following parenteral administration; however, the clinically effective duration of action may be less than an hour (Gutstein and Akil, 2002).

5.2 Toxicokinetics

There were no toxicokinetics studies with naloxone submitted in this NDA.

6 General Toxicology

There were no general toxicology studies with naloxone submitted in this NDA or identified in the literature search.

7 Genetic Toxicology

There were no genetic toxicology studies with naloxone submitted in this NDA or identified in the literature search.

The proposed drug product labeling appears to reflect some of the current generic drug product labels for naloxone. However, the Narcan label was updated in 2001 to include the results of genetic toxicology studies, as follows:

NARCAN was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.

As the studies were likely completed with naloxone hydrochloride, this paragraph will be modified accordingly and should be included in the product labeling. Currently, the Agency prefers not to include language such as “weakly positive” in labeling; however, as the raw data are not available via a 505(b)(2) application, the Narcan labeling will be retained.

8 Carcinogenicity

There were no carcinogenicity studies with naloxone submitted in this NDA or identified in the literature search.

9 Reproductive and Developmental Toxicology

There were no new reproductive and developmental toxicology studies with naloxone submitted in this NDA. A Sponsor identified two articles that evaluated the effects of naloxone on reproductive and developmental endpoints, which are discussed below.

In studies designed to characterize the effect of endogenous opioids release during parturition, Hetta and Terenius treated pregnant rats with naloxone subcutaneously via implanted minipumps that delivered either 0.033 or 0.1 mg/h naloxone continuously for 7 days. Treatment was either begun on Day 11 or 17 of pregnancy or Postnatal Day 3. Treatment with the high dose of naloxone from Day 17 of pregnancy resulted in an increase in the number of stillborn pups and pups that died within 36 hours of birth. Similar results, although not statistically significant, were noted with the lower dose of naloxone. In contrast, naloxone administration from Day 11 to 18 of pregnancy or treatment of dams beginning on Postnatal Day 3 did not alter pup survival rates. These authors also noted that exposure to naloxone during development altered the analgesic response to morphine later in life (Hetta and Terenius, 1980). The high dose of naloxone resulted in 2.4 mg/day or approximately 7 mg/kg (HED of 67.7 mg/60 kg person or ~169 times the single human adult dose of 0.4 mg). Given the difference in the drug dosing regimen employed in this rat study and the clinical exposures that would occur with EVZIO, the clinical significance of these findings is not clear.

Rocha-de-Melo and colleagues treated newborn male rat pups with 10 mg/kg, SC from post-natal Day 7 to 28. Cortical spreading depression (CSD) or the rate of ion-induced neuronal depolarizations that results in waves of neuronal depolarization and propagation across the cortical surface, was measured when the pups were 30-40 days or 90-120 days old. The authors report that naloxone treatment of the rat pups resulted in an impairment of CSD (decreased CSD velocity) later in life (Rocha-de-Melo, et al., 2008). The report does not test lower doses; therefore, a NOAEL level was not determined. The dose tested in the rat pups correlates with a human equivalent dose (HED) of 1.6 mg/kg (based on body surface area comparison in adults), which is approximately ~16 times the 0.4 mg/4 kg neonate dose. Given the differences in dose and the duration of treatment employed in this study, the clinical relevance of this observation for the intended indication is unclear.

Although these studies and others suggest that naloxone exposure during pregnancy and in the early postnatal period may result in changes in the CNS response to opioids, the results are not clinically relevant to the EVZIO dosing regimen proposed. Obviously not treating a pregnant woman or neonate suspected of opioid overdose could result in death; therefore, the data do not change the risk:benefit for this particular drug product.

The proposed drug product labeling includes information found in the referenced product labeling with minor drug product-specific alterations.

The referenced drug product labeling (Narcan) was apparently updated in 2001 to include exposure margins for the reproductive and developmental toxicology studies

completed by the innovator. The Narcan label includes the following statement under the “Impairment of Fertility” subheading:

Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to NARCAN.

As the subheading is impairment of fertility and presumably naloxone hydrochloride was tested in the study rather than the Narcan drug product, the Narcan language will be modified to state naloxone hydrochloride and only discuss fertility effects in this section of the labeling. The embryotoxic and teratogenic references will be retained for the Pregnancy section of the label.

The Narcan labeling changes in 2001 also appear to have resulted in a change in the pregnancy category. Prior to 2001 Narcan was labelled a Pregnancy Category B drug. In 2001, the label was changed to a Pregnancy Category C. It is not clear why this change was made, and it is possible that this was an error, as there is no official record why the category was changed. Specifically, the pharmacology toxicology reviewer who recommended the addition of the exposure margins did not discuss the category. The medical reviewer noted that the drug was previously a Pregnancy Category B drug and did not make any recommended change to this category. The project manager’s review also did not include any documentation suggesting that the category should be changed. However, the approvable letter which was issued for the Narcan labeling supplement included the following statement:

Revise the “Use in Pregnancy-Teratogenic Effects Pregnancy Category C” subsection in the PRECAUTIONS section to read as follows:

Teratology studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to NARCAN.

Careful review of the historical records suggests that this may have been an error and the Sponsor may have logically interpreted the letter to mean that the Agency was recommending a change to the pregnancy category.

Based on the data presented in the Narcan labeling, there were no adverse effects noted in the animal toxicology studies completed. This would suggest that a Pregnancy Category B is appropriate. Although it is possible that the addition of the “weakly positive” genetic toxicology findings may have a change to a Pregnancy Category C; this was not discussed in the reviews completed at the time. Based on the data available, we recommend that Evzio be labeled as a Pregnancy Category B.

10 Special Toxicology Studies

There were no special toxicology studies with naloxone submitted in this NDA.

11 Integrated Summary and Safety Evaluation

The Applicant did not submit any new nonclinical studies to support this marketing NDA. The naloxone drug formulation does not contain any novel excipients. The specifications as proposed for drug substance impurities and drug product degradants meet ICH Q3A(R2) and Q3B(R2) qualification thresholds and are acceptable. The container closure system used in the naloxone autoinjector has been adequately characterized for safety via an extractable study and a leachables assessment in the ongoing stability studies and the levels of leachables found as a result of these studies do not represent a safety concern. The Applicant is referencing the label for Endo's Narcan (NDA 16636) for the information in the Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy sections.

From a nonclinical pharmacology toxicology perspective, the drug product, naloxone autoinjector may be approved with the recommended labeling changes and without any post-marketing nonclinical studies.

12 Appendix/Attachments

Reference List

Ball D, Blanchard J, Jacobson-Kram D, McClellan RO, McGovern T, Norwood DL, Vogel WM, Wolff R, and Nagao L (2007) Development of Safety Qualification Thresholds and Their Use in Orally Inhaled and Nasal Drug Product Evaluation. *Toxicological Sciences* **97**:226-236.

Gutstein HB and Akil H (2002) Opioid Analgesics, in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (Hardman JG, Limbird LE and Gilman AG eds) pp 569-619, McGraw-Hill, New York.

Hetta J and Terenius L (1980) Prenatal naloxone affects survival and morphine sensitivity of rat offspring. *Neurosci Lett* **16**:323-327.

Rocha-de-Melo AP, de Lima KR, de Albuquerque JM, de Oliveira AK, and Guedes RC (2008) Chronic neonatal exposure of rats to the opioid antagonist naloxone impairs propagation of cortical spreading depression in adulthood. *Neurosci Lett* **441**:315-318.

Wang D, Sun X, and Sadee W (2007) Different effects of opioid antagonists on mu-, delta-, and kappa-opioid receptors with and without agonist pretreatment. *J Pharmacol Exp Ther* **321**:544-552.

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/s/

CARLIC K HUYNH
03/20/2014

RICHARD D MELLON
03/20/2014

I concur with Dr. Huynh that NDA 205787 may be approved from a nonclinical pharmacology toxicology perspective. Please refer to the action letter for final drug product labeling.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 205787 **Applicant:** Kaleo, Inc.

Stamp Date: December 20, 2013

Drug Name: Naloxone Auto-Injector (0.4 mg) **NDA/BLA Type:** 505(b)(2)

DAAAP/ODEII/OND/CDER/OMPT/FDA

On **initial** overview of the NDA/BLA application for filing: FILEABLE

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable. The Sponsor did not conduct any new nonclinical studies. The submitted 505(b)(2) New Drug Application (NDA) included referenced nonclinical studies. The Sponsor is referencing NDA 16636 (Endo's Narcan) for the Agency's previous findings of safety. The Sponsor has submitted a literature review for carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. The Sponsor did not conduct any new nonclinical studies. The submitted 505(b)(2) New Drug Application (NDA) included a reference to NDA 16636 (Endo's Narcan).
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Not applicable. The Sponsor did not conduct any new nonclinical studies. The submitted 505(b)(2) New Drug Application (NDA) included a reference to NDA 16636 (Endo's Narcan).

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable. The Sponsor did not conduct any new nonclinical studies. The submitted 505(b)(2) New Drug Application (NDA) included a reference to NDA 16636 (Endo's Narcan).
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		There are no special studies/data requested by the Agency in previous discussions with the Sponsor.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		The Applicant's proposed labeling is the same as the referenced product NDA 16636 for the pharmacology/toxicology sections (carcinogenesis, mutagenesis, teratogenic effects, nonteratogenic effects, and impairment of fertility).
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	<p>DS specifications use both EP <2.2.29> and In house method (b)(4) #940907 analytical methods. Only the In house method (b)(4) #940907 meet ICH Q3A(R2) qualification thresholds of NMT (b)(4)% for drug products with a maximum daily dose of ≤ (b)(4)g/day. The levels of (b)(4) have not changed since the IND submission and are acceptable.</p> <p>DP specifications meet ICH Q3B(R2) qualification thresholds of NMT (b)(4)% for drug products with a maximum daily dose of < 10 mg/day. The levels of 2,2'-binaloxone have been reduced to NMT (b)(4)% as per the preIND meeting minutes.</p> <p>The container closure system has not changed since the IND submission. The container closure is comprised of a glass cartridge (DMF (b)(4)), crimp cap (DMF (b)(4)), and plunger (DMF (b)(4) and (b)(4)). Extractable leachable study may not be needed as the naloxone formulation is comparable to epinephrine.</p>
11	Has the applicant addressed any abuse potential issues in the submission?		X	There are no abuse potential studies submitted in this NDA.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. This is a 505(b)(2) New Drug Application (NDA) submitted to support a Rx.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION
FILEABLE? YES**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

We have no comments for the 74-day letter.

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

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

/s/

CARLIC K HUYNH
01/10/2014

RICHARD D MELLON
01/10/2014