

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205787Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 205787	Submission Date(s): July 19, 2013, November 22, 2013, and December 20, 2013
Proposed Brand Name	EVZIO Naloxone Auto-Injector (NAI)
Generic Name	Naloxone HCl Injection, USP
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Kaleo Inc
Relevant IND(s)	IND 112,292
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Solution for injection; 0.4 mg/0.4 mL
Indication	 (b) (4)

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA submissions dated July 19, 2013, November 22, 2013, and December 20, 2013 and finds them acceptable from clinical pharmacology perspective. OSI reviewers recommend that the data from the clinical and analytical portions of pivotal comparative bioavailability study IJ-900DV-03O are acceptable for Agency review.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Key clinical pharmacology findings:

EVZIO NAI exhibited 15% greater C_{max} and comparable AUC values of naloxone in comparison to the reference (0.4 mg naloxone HCl delivered via a standard syringe).

EVZIO NAI is a single-use auto-injector that delivers 0.4 mg (0.4 mL) naloxone HCl via subcutaneous or intramuscular injection. (b) (4)

Naloxone HCl, which is approved for intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration, is not currently available in an auto-injector. EVZIO NAI is designed to deliver a previously approved formulation and dose of naloxone HCl using approved routes of administration via a user-actuated, single-use auto-injector. 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, sponsor 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. This approach was deemed acceptable per the Agency's advice letter dated May 24, 2012. The IMS product has been approved for IV, IM and SC administration.

The clinical/clinical pharmacology database for this NDA consists of one pivotal comparative bioavailability study (Study IJ-900DV-03O) conducted in 30 healthy volunteers. Because the approved initial dose of Narcan is from 0.4 mg to 2 mg in adults, sponsor conducted the comparative bioavailability study to demonstrate that EVZIO NAI will provide comparable or higher naloxone exposure in comparison to the reference product at the tested dose of 0.4 mg.

Relative Bioavailability of EVZIO NAI in Comparison to the Reference Product

EVZIO NAI exhibited equivalent naloxone AUC_t and AUC_{inf} values in comparison to the reference drug product as the 90% confidence interval (CI) of EVZIO NAI:reference geometric mean ratios for naloxone AUC_t and AUC_{inf} fell within the bioequivalent limits of 80 to 125%. EVZIO exhibited 15% greater C_{max} values than the reference drug product. The medium T_{max} value of naloxone for EVZIO NAI was similar to the reference product (0.25 h vs. 0.33 hr).

2 Question Based Review

2.1 General Attributes of the Drug

1. *What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug product?*

Naloxone HCl is approved for intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration. Narcan (NDA 016636) has been discontinued and is no longer marketed. Generic naloxone HCl products are commercially available in pre-filled syringes and vial. According to Narcan's labeling, Narcan may be administered intravenously, intramuscularly, or subcutaneously. In adults with opioid overdose, an initial dose of 0.4 mg to 2 mg of Narcan may be administered intravenously. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

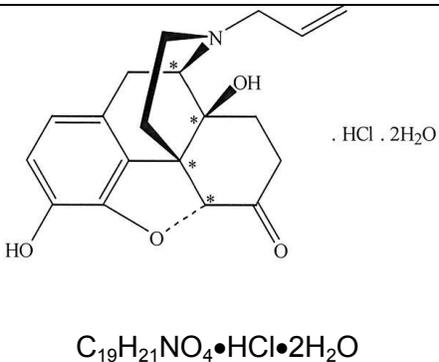
EVZIO NAI is a single-use auto-injector that delivers 0.4 mg (0.4 mL) naloxone HCl via subcutaneous or intramuscular injection. Kaleo Inc submitted a 505(b)(2) NDA 205787 for EVZIO NAI and proposed to rely on the Agency's previous finding of the safety and efficacy of the listed drug, Narcan (NDA 016636).

As indicated in the Agency's comments to regulatory Question #2 at the Pre-IND meeting, for a 505(b)(2) application, the listed drug relied upon for approval must be a product approved under section 505(b) (NDA) of the Food, Drug, and Cosmetic Act. When an ANDA product must be used for a bio-bridging study because the NDA product is no longer available in the market, the Sponsor must identify an NDA product as the listed drug and do a patent certification against that NDA product.

Because the NDA product Narcan is not available, in the pivotal comparative bioavailability Study IJ-900DV-03O, sponsor used the generic product, 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. This approach was deemed acceptable per the Agency's advice letter dated May 24, 2012.

2. What are the highlights of the chemistry and physico-chemical properties of the drug substances, and the formulation of the drug product?

Table 1 Physical-Chemical Properties of Naloxone Hydrochloride

Drug Name	Naloxone Hydrochloride
Chemical Name	17-Allyl-4,5a-epoxy-3,14-dihydroxymorphinan-6 hydrochloride
Structure	 <p style="text-align: center;">$C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$</p>
Molecular Weight	(b) (4)
Appearance	White to off-white powder
Solubility	Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol, and practically insoluble in ether and in chloroform

EVZIO NAI formulation is identical to a listed drug product (International Medicinal Systems, Limited 2 mg/2 mL (single dose disposable LUER-JET prefilled syringe) NDC number: 76329-3369-1, ANDA 072076. The components and compositions of EVZIO NAI formation are listed in **Table 2**.

The device component of EVZIO NAI is a (b) (4), needle-based system that delivers the prescribed dose of naloxone HCl into the user. When activated, EVZIO NAI will inject a single dose of 0.4 mg of naloxone HCl (0.4 mL). EVZIO NAI is designed to be a single use device.

Table 2 Components and Composition of EVZIO NAI

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			

3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

While the mechanism of action of naloxone is not fully understood, evidence suggests that naloxone antagonizes the opioid effects by competing for the same receptor sites.

EVZIO NAI is indicated for.

- [Redacted] (b) (4)
- [Redacted] (b) (4)

4. What are the proposed dosage(s) and route(s) of administration?

An initial dose of 0.4 mg of naloxone hydrochloride may be administered intramuscularly or subcutaneously using EVZIO NAI. 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.

2.2 General Clinical Pharmacology

1. What is known about the PK characteristics of naloxone for the listed drug, Narcan?

Following parenteral administration naloxone hydrochloride is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation, and excreted in urine. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ±

12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours.

2. What moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?

Naloxone and total naloxone (free naloxone plus naloxone-3 β -glucuronide) are measured in the pivotal PK study.

2.3 Intrinsic Factors

1. What is the pediatric plan?

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4) Clinical team and PeRC do not agree with the Applicant's (b) (4) request and believe that, given the safety margin of naloxone, NAI can be labeled for all pediatric age ranges.

2.4 General Biopharmaceutics

1. What are the relative bioavailabilities of naloxone following the administration of EVZIO NAI in comparison to the reference, injection via standard syringe?

EVZIO NAI exhibited equivalent naloxone AUC_t and AUC_{inf} values in comparison to the reference product using standard syringe. A 15% higher C_{max} values was observed following the EVZIO NAI injection compared to the reference.

The relative bioavailability of naloxone following the administration of EVZIO NAI in comparison to the reference drug were evaluated in a randomized, fasting, 2-period cross-over study (Study IJ-900DV-03O) in 30 healthy subjects. Subjects were randomized to receive either test investigational medicinal product (IMP) (single injection

of 0.4 mg naloxone HCl for injection administered using EVZIO NAI) or reference IMP (single injection of 0.4 mg naloxone HCl for injection administered using a standard syringe) on consecutive days. Dosing was performed by trained, qualified personnel designated by the Principal Investigator. The test or reference product was administered via injection into mid-anterolateral thigh on the morning of Day 1 according to randomization. The alternate treatment was administered via injection into the same mid-anterolateral thigh on the morning of Day 2. Sponsor stated that the injection process for the test and reference product consisted of full insertion of the exposed needle length at a 90 degree angle to the injection site (into the mid-anterolateral thigh) prior to expulsion of the naloxone formulation through the needle into the tissue. The issue layer location (i.e., subcutaneous space vs. intramuscular space) for the injection was dependent on the depth of fat under the skin and overlying the muscle and independent of the injection process. The needle length for EVZIO NAI is a nominal 0.5" and the needle length for the reference was 5/8", according to the information provided in the study manual. Blood samples were collected at 5 min prior to dosing and 5, 10, 15, 20, 30, 40, and 50 minutes and 1, 1.25, 1.5, 2, 3, 4, and 6 hours post-dose for each dosing period.

The naloxone plasma concentration-time profiles are shown in **Figure 1**. The median T_{max} values are similar for both treatments (0.25 h vs. 0.33 h). The statistical analysis results for the assessment of relative bioavailability are presented in the **Table 3**. EVZIO NAI exhibits equivalent AUC_t and AUC_{inf} values in comparison to reference as the 90% CIs of EVZIO NAI:reference geometric mean ratios for naloxone AUC_t and AUC_{inf} values fell within the bioequivalence limits of 80 to 125%. A 15% greater C_{max} values is observed for EVZIO NAI compared to reference product. The geometric mean ratio is 1.15 with a 90% CI of (0.97, 1.37). The half-life values following administration of EVZIO NAI are similar the reference product (1.28 hr vs. 1.36 hr). The total naloxone plasma concentration-time profiles are shown in **Figure 2**. Consistent with naloxone data, total naloxone C_{max} values following the administration of EVZIO NAI appears to be higher.

Figure 1 Mean naloxone plasma concentration (ng/mL) time profiles following the administration of EVZIO NAI and Reference (0.4 mg injection via standard syringe) (N = 30)

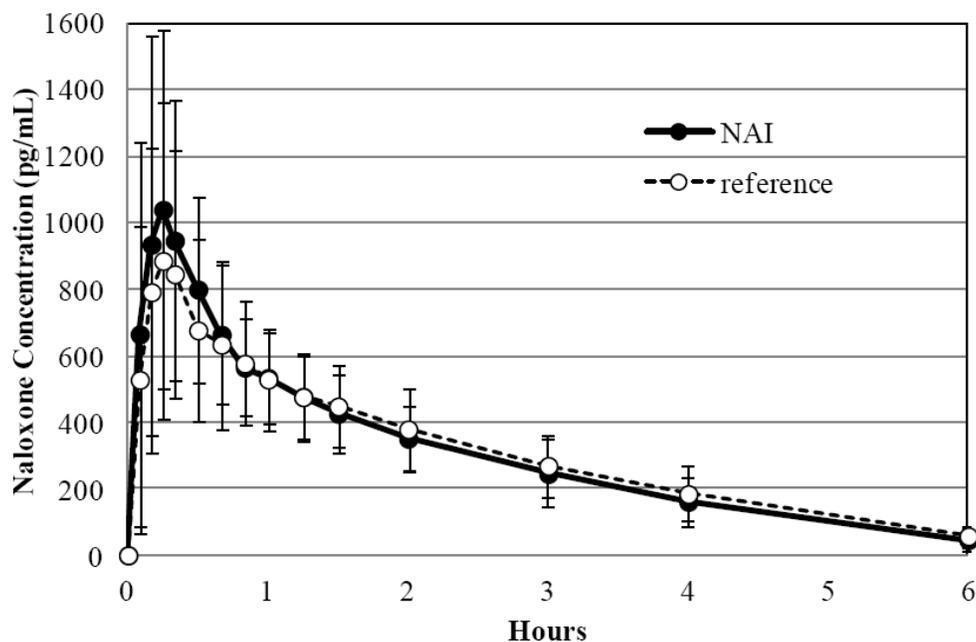
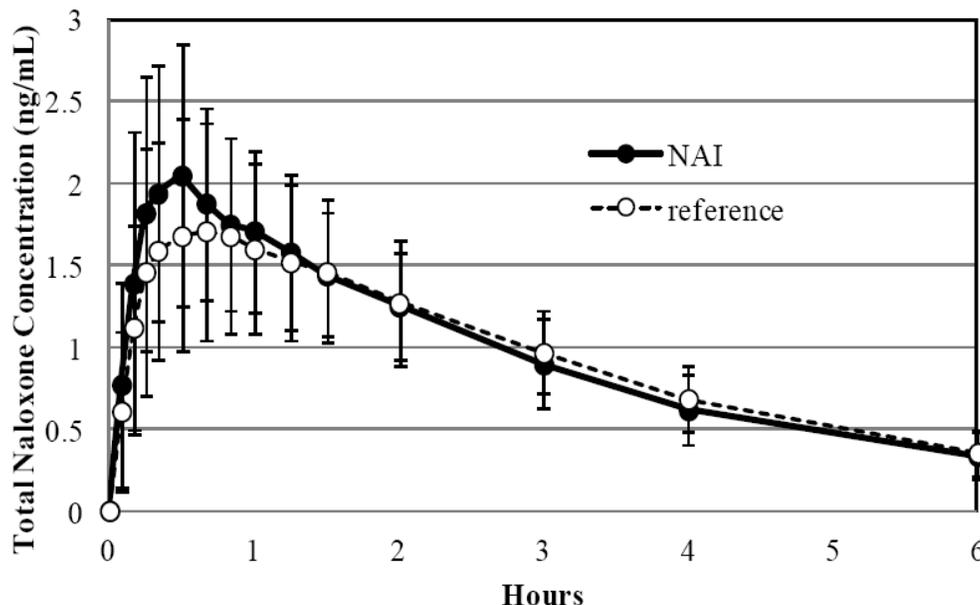


Table 3 Naloxone PK parameters following 0.4 mg naloxone injection via EVZIO NAI (Test IMP) and standard syringe (Reference IMP) and statistical analysis

Treatment	Statistic	C _{max} (pg/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-t} (pg.h/mL)	AUC _{0-inf} (pg.h/mL)
Test IMP	Mean ± SD	1240 ± 638		1.28 ± 0.485	1830 ± 397	1930 ± 453
	%CV	51.4		38.0	21.7	23.4
	Median (Min-Max)	1070 (471-3110)	0.25 (0.08-1.23)	1.20 (0.885-3.13)	1790 (898-2680)	1910 (932-2960)
Reference IMP	Mean ± SD	1070 ± 482		1.36 ± 0.319	1850 ± 452	1980 ± 495
	%CV	45.1		23.5	24.4	25.0
	Median (Min-Max)	959 (294-2270)	0.33 (0.08-2.03)	1.28 (0.894-2.35)	1760 (859-3040)	1840 (922-3100)
	Treatment Ratio (Test/Reference)	1.15			0.993	0.983
	90% CI for Ratio	0.97, 1.37			0.94, 1.05	0.937, 1.03

Figure 2 Total Naloxone concentration time profiles following the administration of EVZIO NAI and Reference (0.4 mg injection via standard syringe)



OSI inspected the clinical and analytical sites of this pivotal comparative bioavailability study IJ-900DV-03O and OSI reviewers recommend that the data from the clinical and analytical portions of pivotal comparative bioavailability study IJ-900DV-03O are acceptable for Agency review.

2.5 Analytical Section

1. *Do the bioanalytical methods adequately validated for determining plasma concentrations of naloxone and total naloxone?*

Validated LC/MS/MS methods were used for the determination of unconjugated naloxone and total naloxone (including both unconjugated naloxone and naloxone conjugates) in human plasma. The assay precision and accuracy of the analytical methods are summarized in **Table 4**.

Table 4 Naloxone Assay Precision and Accuracy

	Free naloxone	Total naloxone
Nominal range for the calibration curve	2 – 1000 pg/mL	100 – 100,000 pg/mL

LLOQ	2 pg/mL	100 pg/mL
QC	5.0, 12.0, 45.0, 160, 750 pg/mL	0.300, 0.750, 3.00, 12.0, and 75.0 ng/mL
Precision (%CV)	2.67 – 5.1%	3.79 – 6.98
Accuracy (% difference from theoretical)	- 6.63 – - 4.96	-2.24 – 5.68

3 Labeling Recommendations

(~~RED Strikeout~~ text should be removed from labeling; Blue double underlined text should be added to labeling)

The following edits are per discussion within the review team and as of today (3/20/14) labeling negotiation with sponsor is still ongoing.

Under Section 8 USE IN SPECIFIC POPULATIONS

8.5 Hepatic Impairment

The safety and effectiveness of EVZIO in patients with hepatic impairment have not been established. Naloxone is mainly metabolized in the liver. The systemic exposure of naloxone can be higher in patients with hepatic impairment due to reduced naloxone metabolism.

8.6 Renal Impairment

The safety and effectiveness of EVZIO in patients with renal impairment have not been established. Naloxone and its metabolites are mainly excreted by the kidney. The systemic exposure of naloxone can be higher in patients with renal impairment due to reduced excretion.

8.7 Geriatric Use

Geriatric patients have a greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Therefore, the systemic exposure of naloxone can be higher in these patients.

Under Section 12 CLINICAL PHARMACOLOGY:

[REDACTED] (b) (4)

(b) (4)

(b) (4)

12. 1 Mechanism of Action

(b) (4)
(b) (4)
antagonizes (b) (4) Naloxone hydrochloride is an opioid antagonist that (b) (4)
(b) (4) opioid effects by competing for the same receptor sites.

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

12.2 Pharmacodynamics

When naloxone hydrochloride is administered intravenously the onset of action is generally apparent within two minutes (b) (4). The time to onset of action is (b) (4) shorter for intravenous compared to (b) (4) subcutaneous (b) (4) or intramuscular routes of administration (b) (4).

The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride. (b) (4)

(b) (4)

12.3 Pharmacokinetics

(b) (4)

In one pharmacokinetic study in 30 healthy subjects, a single EVZIO injection provides equivalent naloxone AUC and 15% greater naloxone Cmax in comparison to a single dose of 0.4 mg naloxone injection using a standard syringe.

Following a single EVZIO injection, the median Tmax of naloxone was reached at 15 min (range 5 minutes to 1.23 hours), with a mean (+ SD) Cmax value of 1.24 (+ 0.64) ng/mL. The mean (+ SD) plasma half-life of naloxone in healthy adults was 1.28 (+ 0.48) hours. In the same study, following administration of a single dose of 0.4 mg naloxone injection using a standard syringe, the median Tmax was 20 minutes (range 5 minutes to 2.03 hours) and the mean (+ SD) Cmax value was 1.07 (+ 0.48) ng/mL. The mean (+ SD) plasma half-life was 1.36 (+ 0.32) hours.

(b) (4)

Distribution

Following parenteral administration, naloxone is distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

Metabolism

Naloxone is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucuronide as the major metabolite.

Elimination

After an oral or intravenous dose, about 25-40% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours. Following a single EVZIO injection, the mean (\pm SD) plasma half-life of naloxone in healthy adults was 1.28 (\pm 0.48) hours. In a neonatal study the mean plasma half-life was observed to be 3.1 \pm 0.5 hours. In a neonatal study the mean plasma half-life was observed to be 3.1 \pm 0.5 hours.

4 Appendix

4.1 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information		Information	
NDA/BLA Number	205-787	Proposed Brand Name	EVZIO 0.4 mg Naloxone Auto-Injector	
OCP Division (I, II, III, IV, V)	II	Generic Name	Naloxone HCl injection, USP	
Medical Division	DAAAP	Drug Class		
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	(b) (4)	
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form, Strength	Solution for injection, 0.4 mg/0.4 mL	
Pharmacometrics Reviewer	N/A	Dosing Regimen	Opioid antagonist	
Date of Submission	July 19, 2013 and Nov 22, 2013, and Dec 20, 2013	Route of Administration	IM or SC injection	
Primary Review Goal Date (GRMP)	May 27, 2014	Sponsor	Kaleo Inc	
		Priority Classification	Priority/Fast Track	
PDUFA Due Date	June 20, 2014	Relevant INDs	IND 112292	
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		Single pilot relative BA study IJ-900DV-03O
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	x	(1)		See above
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	To be marketed formulation was used in the relative BA study
2	Has the applicant provided metabolism and drug-drug interaction information?			√	No new findings in the proposed label.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			Relative BA study was conducted with a generic drug product (ANDA 72076) since the NDA product Narcan (NDA 016636) is discontinued (not due to safety or effectiveness reason).
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?			√	Match the exposure of the list drug
6	Is the clinical pharmacology and biopharmaceutics section of the NDA	√			

	organized, indexed and paginated in a manner to allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	√			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			√	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	Submitted pediatric plan
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet	√			

	basic requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

This NDA is fileable from clinical pharmacology perspective. OSI inspection request for the pivotal relative BA study IJ-900DV-03O was sent on January 2nd, 2014. The requested action goal date is March 15, 2014.

If the NDA/BLA is not fileable from the clinical pharmacology 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.

There are no comments for sponsor at this time.

 Reviewing Clinical Pharmacologist Date

 Team Leader/Supervisor Date

Background:

Kaleo Inc submitted a 505(b)(2) NDA 205787 for naloxone HCl auto-injector 0.4 mg (NAI) for IM or SC administration. (b) (4)

(b) (4)

This NDA relies on the Agency's previous findings of safety and effectiveness for Narcan (NDA 016636). Since Narcan is discontinued, sponsor used a generic drug product (ANDA 72076) in the pivotal relative BA study IJ-900DV-03O. The to-be-marketed formulation was used in the relative BA study.

Study IJ-900DV-03O is randomized, single-dose, single-blind, two-sequence, two-period crossover BA, safety and tolerability study in healthy subjects. In this study, naloxone HCl delivered via NAI was demonstrated to have 15% higher C_{max} and comparable AUC values to the reference (naloxone HCl delivered via standard syringe).

4.2 Individual Study Summary

Intelliject, Inc.
IJ-900DV-03O

Clinical Study Report
CONFIDENTIAL

2 SYNOPSIS

Name of Sponsor/Company: Intelliject, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Not applicable		
Name of Active Ingredient: Naloxone hydrochloride		
Title of Study:	A Randomized, Single-Blind, Two-Sequence, Two-Period Comparative Bioavailability Study of Two Naloxone Hydrochloride Products in Healthy Human Volunteers	
Principal Investigator:	Ronald Goldwater MDCM, MSc (A)	
Study Center:	PAREXEL Early Phase Clinical Unit, Baltimore	
Publication:	None at the time of writing this clinical study report	
Development Phase:	Phase 1 comparative bioavailability and safety study	
Studied Period:	First subject first visit:	08 January 2013
	Last subject last visit:	26 February 2013
Study Objectives:	<p>The primary objective of the study was:</p> <ul style="list-style-type: none"> To compare the pharmacokinetics (PK) of 0.4 mg naloxone hydrochloride (HCl) following a single intramuscular (IM) or subcutaneous (SC) injection administered using either the naloxone auto-injector (NAI) or a standard syringe. <p>The secondary objective of the study was:</p> <ul style="list-style-type: none"> To assess the safety and tolerability of naloxone HCl injection by NAI compared to standard syringe. 	
Study Design:	<p>This was a randomized, single-blind, single-dose, two-sequence, two-period crossover bioavailability, safety and tolerability study in fasted, healthy, male and female subjects to evaluate the PK of naloxone administered by injection using either NAI or a standard syringe. Thirty (30) healthy adult subjects were enrolled and received the investigational medicinal product (IMP) in the study. The duration of study participation for each subject was less than 5 weeks (up to 4 weeks for the Screening period and 3 days for in-patient admission to complete the two dosing periods).</p>	
Methodology:	<p>Subjects were randomized to receive one of the following treatments on Day 1 and the alternate treatment on Day 2:</p> <ul style="list-style-type: none"> Test IMP: A single injection of 0.4 mg naloxone HCl for injection United States Pharmacopeia (USP) administered using NAI. Reference IMP: A single injection of 0.4 mg naloxone HCl for injection USP administered using a standard syringe. <p>During Screening (Day -28 to Day -2), subjects signed the informed consent and then underwent procedures to determine eligibility. Eligible subjects reported to the clinical unit on the day prior to first dose administration and remained in the clinical unit until the final post-dose blood sample was collected and all discharge procedures were completed for the second dosing period. In one dosing period, subjects received the Test IMP; in the other period, subjects received the Reference IMP. The order of treatments was randomly assigned. There was a washout period between the two dosing periods of at least 24 hours.</p> <p>Safety assessments were conducted throughout the study. At the completion of Day 2 (i.e., after receiving the second dose of IMP and providing the last PK sample), subjects received a physical examination, a pregnancy test (females of childbearing potential only), underwent routine clinical laboratory assessments (hematology, clinical chemistry, urinalysis), 12-lead electrocardiogram (ECG), vital sign assessments and injection site evaluation before discharge from the clinical unit.</p>	

Name of Sponsor/Company: Intelliject, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)		
Name of Finished Product: Not applicable				
Name of Active Ingredient: Naloxone hydrochloride				

Number of Subjects (Planned and Analyzed):		
	Safety Population	Pharmacokinetic Population
Planned	30	30
Included	30	30
Evaluable	30	30

Inclusion Criteria:

- Male or female subjects between the age of 18 and 45 years (inclusive) at Day -1 (admission).
- Subjects who were willing and able to understand and provide written informed consent to participate in the study.
- Subjects who were willing and able to participate in all required study activities for the entire duration of the study.
- At Day -1 (admission), subjects had a body mass index between 18.5 and 29.9 kg/m², inclusive and a weight \geq 50 kg and \leq 100 kg.
- Female subjects were either post-menopausal (defined as at least 2 years without any menses) prior to Screening or were documented as surgically sterile (at least 1 month before Screening).
OR
If of childbearing potential (defined as not surgically sterile at least 1 month before Screening and pre-menopausal or <2 years post-menopausal), must have had negative pregnancy tests at Screening and Day -1 (admission) and must have been using highly effective contraception (defined as established, consistent use of oral, injected or implanted hormonal methods of contraception established for at least 90 days before Day -1 [admission] and committed to continue its use for 28 days after final IMP administration, placement of an intrauterine device or intrauterine system, barrier methods of contraception such as condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository), double-barrier method or abstinence.
- Male subjects and their female spouses/partners of childbearing potential must have been using highly effective contraception consisting of two forms of birth control (one of which must have been a barrier method) which started at Screening and committed to continue its use for 28 days after final IMP administration.
- No clinically significant abnormal findings on physical examination, medical history, ECG or clinical laboratory results during Screening or Day -1 (admission).
- Blood pressure, pulse and other vital signs were within clinically acceptable ranges at Screening and Day -1 (admission).

Identity of Investigational Medicinal Products:

IMP	Name	Strength	Route	Manufacturer
Test	Naloxone Auto-Injector	1.0 mg/mL naloxone HCl	IM or SC	Sponsor
Reference	Naloxone HCl for Injection USP	1.0 mg/mL naloxone HCl	IM or SC	International Medicinal Systems (IMS), Limited

HCl = Hydrochloride; IM = Intramuscular; SC = Subcutaneous; USP = United States Pharmacopeia

Duration of Treatment:
Subjects received two doses of IMP, either the Test or the Reference on Day 1 and the alternate product on Day 2.

Treatment Compliance:
Dosing was performed by trained, qualified personnel designated by the Principal Investigator. The date and time of dosing were documented on each dosing day. No deviations from the planned dosing procedures were noted. Compliance was also ensured by Sponsor audit of the source documents.

Name of Sponsor/Company: Intelliject, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Not applicable	Volume:	
Name of Active Ingredient: Naloxone hydrochloride	Page:	
Criteria for Evaluation:		
Pharmacokinetics:		
<p>Blood (approximately 7 mL) was collected 5 minutes prior to dosing and at 5, 10, 15, 20, 30, 40 and 50 minutes and 1, 1.25, 1.5, 2, 3, 4 and 6 hours post-dose for each dosing period.</p>		
<p>The following PK parameters were estimated from naloxone concentrations: maximum plasma naloxone concentration determined directly from the concentration-time profile (C_{max}); time of maximum plasma naloxone concentration determined directly from the concentration-time profile (T_{max}); area under the concentration-time curve (AUC) from pre-dose (time 0) to the time of the last quantifiable concentration (T_{last}) (AUC_{0-t}); AUC from pre-dose (time 0) extrapolated to infinity (AUC_{0-inf}); apparent terminal elimination rate constant (λ_{z}) and terminal elimination half-life ($T_{1/2}$).</p>		
Safety:		
<p>Routine safety monitoring was conducted during the in-house phase of the study. Safety and tolerability was evaluated by physical examinations, clinical laboratory tests (i.e., hematology, chemistry and urinalysis), vital sign assessments, ECGs, injection site assessment and monitoring of adverse events (AEs) and concomitant medications.</p>		
Statistical Methods:		
<u>Sample size considerations:</u>		
<p>The sample size estimate was based on PK data obtained in 6 subjects following IM administration of 0.8 mg naloxone HCl. From these data, 18 subjects were estimated to provide 90% statistical power for testing whether the confidence intervals (CIs) for the bioequivalence (BE) ratios (ratios of means of C_{max} and AUC) lie within the limits (0.80, 1.25). To allow for imprecision of sample size estimation, 30 subjects were enrolled in the study.</p>		
<u>Data presentations/Descriptive statistics</u>		
<p>All demographic, safety, bioavailability and PK data were listed and summarized in tabular format using descriptive statistics, as appropriate. Pharmacokinetic data were also displayed graphically.</p>		
<u>Statistical analyses</u>		
<p>For naloxone C_{max}, AUC_{0-t} and AUC_{0-inf}, a mixed model analysis of variance (ANOVA) was applied to the logarithmically-transformed data and used to test the significance of the effects of sequence, period and treatment. Subject nested within sequence was assumed to be a random effect; sequence, period and treatment were modeled as fixed factors. The treatment ratios (Test IMP/Reference IMP) for C_{max}, AUC_{0-t} and AUC_{0-inf} were calculated by taking the anti-logarithm of the difference between treatment means. A 90% CI for each treatment ratio was obtained by taking the anti-logarithm of the 90% CI endpoints for the mean difference.</p>		
Pharmacokinetic Results:		
<p>For both AUC_{0-t} and AUC_{0-inf}, the Test IMP is bioequivalent to the Reference IMP, and inter-subject variability in AUC is similar across products. The respective geometric means (percentage coefficient of variation [%CV]) of AUC_{0-inf} after dosing with the Test and the Reference IMP are 1880 pg.h/mL (24.7%) and 1910 pg.h/mL (27.5%). The geometric mean ratios and associated 90% CIs for the AUC parameters fell within the traditional bioequivalence acceptance limits of 0.8 to 1.25.</p>		
<p>Although similar, C_{max} for the Test IMP was not found to be bioequivalent to the Reference IMP. The respective geometric means (%CV) for C_{max} following dosing with the Test and the Reference IMPs were 1100 pg/mL (52.4%) and 957 pg/mL (53.2%). The geometric mean ratio was 1.15 with a 90% CI of (0.97, 1.37).</p>		
<p>Median T_{max} is similar after dosing with the Test IMP compared to the Reference IMP. The median (range) T_{max} values following the Test IMP and the Reference IMP are 0.25 hour (0.08 – 1.23 hours) and 0.33 hour (0.08 – 2.03 hours), respectively.</p>		
<p>Median $T_{1/2}$ is similar for the two IMPs; geometric mean $T_{1/2}$s are 1.22 hours and 1.32 hours after dosing with the Test and Reference IMPs, respectively.</p>		

Name of Sponsor/Company: Intelliject, Inc.		Individual Study Table Referring to Part of the Dossier			(For National Authority Use Only)		
Name of Finished Product: Not applicable							
Name of Active Ingredient: Naloxone hydrochloride							
		Volume:					
		Page:					
Summary Naloxone Plasma Pharmacokinetic Parameters							
Treatment	Statistic	C_{max} (pg/mL)	T_{max} (h)	T_½ (h)	λ_z (1/h)	AUC_{0-t} (pg.h/mL)	AUC_{0-inf} (pg.h/mL)
Test IMP	n	30	30	30	30	30	30
	Mean	1240		1.28	0.588	1830	1930
	SD	638		0.485	0.136	397	453
	%CV	51.4		38.0	23.2	21.7	23.4
	Median	1070	0.25	1.20	0.577	1790	1910
	Min	471	0.08	0.885	0.221	898	932
	Max	3110	1.23	3.13	0.783	2680	2960
	Geometric %CV	52.4		29.2	29.2	23.1	24.7
Geometric Mean	1100		1.22	0.569	1780	1880	
Reference IMP	n	30	30	30	30	30	30
	Mean	1070		1.36	0.535	1850	1980
	SD	482		0.319	0.110	452	495
	%CV	45.1		23.5	20.6	24.4	25.0
	Median	959	0.33	1.28	0.542	1760	1840
	Min	294	0.08	0.894	0.295	859	922
	Max	2270	2.03	2.35	0.776	3040	3100
	Geometric %CV	53.2		22.0	22.0	26.9	27.5
Geometric Mean	957		1.32	0.524	1800	1910	
h= hour(s); SD = Standard Deviation; %CV = Percentage coefficient of variation							

Name of Sponsor/Company: Intelliject, Inc.		Individual Study Table Referring to Part of the Dossier		(For National Authority Use Only)			
Name of Finished Product: Not applicable							
Name of Active Ingredient: Naloxone hydrochloride							
		Volume:					
		Page:					
Statistical Analysis of Relative Bioavailability for Naloxone Plasma Pharmacokinetic Parameters							
Parameter (unit)	IMP	N	Geometric LS Means	Geometric LS Means 95% CI	Treatment Ratio (Test/Reference)	90% CI for Ratio of Geometric LS Means	Within Subject %CV
C _{max} (pg/mL)	Test	30	1100	(918, 1320)	1.15	(0.97, 1.37)	40.9
	Reference	30	957	(797, 1150)			
AUC ₀₋₄ (pg.h/mL)	Test	30	1780	(1620, 1960)	0.993	(0.94, 1.05)	12.6
	Reference	30	1800	(1640, 1970)			
AUC _{0-inf} (pg.h/mL)	Test	30	1880	(1710, 2070)	0.983	(0.937, 1.03)	10.9
	Reference	30	1910	(1740, 2110)			
CI = Confidence interval; %CV = Percentage coefficient of variation; LS: Least squares; N = Number of subjects exposed to treatment							
Safety Results:							
In general, naloxone HCl administered using either NAI or a standard syringe was well-tolerated by healthy subjects in this study.							
Overall, 13 TEAEs were reported for 10 subjects during the study (7 TEAEs reported for 5 subjects after administration of the Test IMP; 6 TEAEs reported for 5 subjects after administration of the Reference IMP). All of the TEAEs were considered by the Investigator to be of mild intensity. Nine (9) of the 13 TEAEs reported were considered by the Investigator to be unrelated to the IMP.							
There were no clinically significant clinical safety laboratory values, vital signs, ECGs values or physical examinations findings. One (1) subject reported injection site pain after administration of the Reference IMP.							
There were no serious adverse events (SAEs), and no AEs led to discontinuation of the IMP.							
Conclusion:							
<ul style="list-style-type: none"> The bioavailability of 0.4 mg naloxone HCl delivered via auto-injector (Test IMP) is comparable to the bioavailability of 0.4 mg naloxone HCl delivered via standard syringe (Reference IMP). Both products were well-tolerated with no safety concerns. 							
Date of Report: Final 1.0, 13 June 2013							
This study was conducted in compliance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki.							

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

/s/

WEI QIU
03/20/2014

YUN XU
03/20/2014

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 205787

2. DATES AND GOALS:

Letter Date: December 20, 2013	Submission Received Date : December 20, 2013
PDUFA Goal Date: June 20, 2014	January 15, 2014

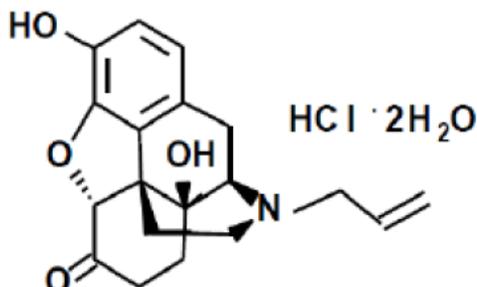
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Naloxone Autoinjector
Established or Non-Proprietary Name (USAN):	Naloxone Autoinjector
Dosage Form:	Injectable
Route of Administration	Injectable
Strength/Potency	0.4mg/0.4ml
Rx/OTC Dispensed:	Rx

INDICATION:

Naloxone Autoinjector (NAI) is a combination drug-device product (b) (4)

4. DRUG SUBSTANCE STRUCTURAL FORMULA: MW: (b) (4)



5. NAME OF APPLICANT (as indicated on Form 356h):

Intelliject, Inc
111 Virginia Street, Suite 405

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Richmond VA 23059

6. SUBMISSION PROPERTIES:

Review Priority:	Priority Review
Submission Classification (Chemical Classification Code):	
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAAAP

7. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		EES entered January 10, 2014 by Luz Riviera
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	
CDRH	X		
Other	X		Microbiology Consult Sent: January 8, 2014 Jessica Cole is the assigned Micro. Reviewer

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes <input checked="" type="checkbox"/> No
CMC Filing Issues: None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes <input checked="" type="checkbox"/> No
CMC Comments for 74-Day Letter: <ol style="list-style-type: none">1. Batch data and stability data do not support the proposed higher specifications noted in the related substances of the drug product than those noted in the related substances in the drug substance, at release and on stability. Tighten the specifications or provide adequate justification for the higher limits proposed in the drug product.2. Clarify the data entry for "Total Impurities" in Table 3.2.P.5.4.3. Batch Analysis of the Drug Product, which lists the total impurities as NMT^(b)₍₄₎% when all the controlled impurities are all at or below the LOQ .3. Explain why in Table 3.2.P.5.4.4 Batch Analysis of the Drug Product, testing for two impurities was not implemented.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes No
Biopharmaceutics Filing Issues: N/A (Email to T. Ghosh, no reviewer assigned)
No Biopharmaceutics Review Attached.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes No
Biopharmaceutics Comments for 74-Day Letter: None

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes <input checked="" type="checkbox"/> No
Microbiology Filing Issues: None
See Microbiology Filing Review by Jessica Cole

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Yes	No	X
Suggested expertise for team:			
CDRH Consult has been requested. The drug product is contained within an auto-injector device comprising software for administration of the dose.			

Summary of Critical Issues and Complexities

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Initial Quality Assessment

Naloxone Auto-injector (NAI) is a combination drug-device product, to be used as a single-use injection to deliver 0.4mg of naloxone hydrochloride (HCl) either subcutaneously or intramuscularly. NAI is filled in a Type I (b) (4) glass cartridge and enclosed by an (b) (4) plunger and (b) (4) lined crimp cap as the primary container closure system. (b) (4)

NAI is intended for persons at risk of serious opioid-related toxicity due to opioid exposure, including overdose. This NDA has been granted a Fast-Track, High Priority Status by the Division.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		All facilities for DS and DP are listed at the end of the document.
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12	Does the section contain a description of the DS manufacturing process?		x	Referenced to DMF (b) (4)
13	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMF (b) (4)
14	Does the section contain information regarding the characterization of the DS?			Referenced to DMF (b) (4)
15	Does the section contain controls for the DS?		x	Referenced to DMF (b) (4)
16	Has stability data and analysis been provided for the drug substance?		x	Referenced to DMF (b) (4)
17	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Naloxone HCl – API Specifications

Table 3.2.S.4.1–1: Specifications for Naloxone Hydrochloride Dihydrate

Test	Method	Specification
Appearance	In house method	White or almost white powder
Appearance of Solution	EP<2.2.1 & 2.2.2 Method II>	Clear
Degree of Clarity		Colorless
Degree of Coloration		
Identification (b) (4)	USP<197K>	Matches standard
Identification B (b) (4)	EP<2.2.27>	Matches standard
Identification (b) (4)	EP<2.3.1>	White precipitate
Specific Rotation (b) (4)	USP<781S>	(b) (4)
Specific Optical Rotation (b) (4)	EP<2.2.7>	(b) (4)
Melting Range	USP <741> Method Ia	
Assay (b) (4)	Naloxone HCl USP monograph	(b) (4) %
Assay (b) (4)	Naloxone HCl EP monograph	(b) (4) 102.0%
Loss on Drying (b) (4), (C)	USP<731>	(b) (4) % max
Water	EP<2.5.12>	(b) (4) %
Sieve Test	US Std. No. 40	(b) (4) through
Chloride Content (b) (4)	Naloxone HCl USP monograph	(b) (4) %
Acidity or Alkalinity	Naloxone HCl EP monograph	(b) (4) nL max
Sulphated Ash	EP<2.4.14>	(b) (4) % max
(b) (4) and Other	Naloxone HCl USP monograph	(b) (4) % maximum
Impurities		
Related Substances	EP<2.2.29>	(b) (4) % max
(b) (4)		(b) (4) % max
(b) (4)		(b) (4) % max
(b) (4)		(b) (4) % max
(b) (4)		(b) (4) % max
(b) (4)		(b) (4) % max
(b) (4)		(b) (4) % max
Unknown Related Substances (each)		(b) (4) % max
Total Related Substances		(b) (4) % max
Assay	In house method (b) (4) #940907	(b) (4) % w/w
Naloxone		(b) (4) % w/w max
(b) (4)		(b) (4) % w/w max
(b) (4)		(b) (4) % w/w max
(b) (4)		(b) (4) % w/w max
(b) (4)		(b) (4) % w/w max
Unknown Related Substances (each)		(b) (4) % w/w max
Total Related Substances		(b) (4) % w/w max
Identification (b) (4)		(b) (4) % w/w max
(b) (4)	In house method (b) (4) #777	(b) (4) % w/w max

Table 3.2.S.4.1–2: Incoming Inspections for Naloxone Hydrochloride Dihydrate

Test	Method	Specification
Identification (IR)	USP	Matches standard
Appearance	USP	White to slightly off white powder
Loss on Drying	USP	NMT (b) (4) %

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Drug Product Composition:

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) ng/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

Drug Product Release Specifications for are shown below.

Table 3.2.P.5.1-1. Quality Control Specifications

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)	X ^a	
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3)	(b) (4)	X ^a	X

ONDQA Initial Quality Assessment (IQA) and Filing Review For Pre-Marking Applications

Table 3.2.P.5.1-1. Quality Control Specifications (continued)

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

^a Results taken from testing conducted on the Drug Cartridge Assembly.

^b Device Performance Specification; Not applicable to Drug Constituent Component.

^c Results taken from Drug Constituent Component release testing at (b) (4) (Section 3.2.P.3.4).

F. METHODS VALIDATION (MV)

	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		X	

G. MICROBIOLOGY

	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		

H. MASTER FILES (DMF/MAF)

	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		LOAs for all pertinent DMFs are provided.

I. LABELING

	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Manufacturing Facilities for Drug Substance and Drug Product:

Drug substance Manufacturer is :

(b) (4)

Drug Product Manufacturing Sites

Table 3.2.P.3.1-1. Manufacturing Sites of the Drug Constituent Component of NAI

Site name and Address	Responsibilities
(b) (4)	
Intelliject, Inc. 111 Virginia Street, Suite 405 Richmond, VA 23229	• Final product approval

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page

NAME : Julia Pinto, Ph.D.

CMC-Lead

Division III

Office of New Drug Quality Assessment

{See appended electronic signature page}

NAME: Prasad Peri, Ph.D.

Branch Chief or Designee

Division III

Office of New Drug Quality Assessment

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

/s/

JULIA C PINTO
02/06/2014

PRASAD PERI
02/10/2014
I concur

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information			Information
NDA/BLA Number	205-787	Proposed Brand Name	EVZIO 0.4 mg Naloxone Auto-Injector	
OCP Division (I, II, III, IV, V)	II	Generic Name	Naloxone HCl injection, USP	
Medical Division	DAAAP	Drug Class		
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	(b) (4)	
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form, Strength	Solution for injection, 0.4 mg/0.4 mL	
Pharmacometrics Reviewer	N/A	Dosing Regimen	Opioid antagonist	
Date of Submission	July 19, 2013 and Nov 22, 2013, and Dec 20, 2013	Route of Administration	IM or SC injection	
Primary Review Goal Date (GRMP)	May 27, 2014	Sponsor	Kaleo Inc	
		Priority Classification	Priority/Fast Track	
PDUFA Due Date	June 20, 2014	Relevant INDs	IND 112292	
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		Single pilot relative BA study IJ-900DV-030
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	x	(1)		See above
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	To be marketed formulation was used in the relative BA study
2	Has the applicant provided metabolism and drug-drug interaction information?			√	No new findings in the proposed label.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			Relative BA study was conducted with a generic drug product (ANDA 72076) since the NDA product Narcan (NDA 016636) is discontinued (not due to safety or effectiveness reason).
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?			√	Match the exposure of the list drug
6	Is the clinical pharmacology and biopharmaceutics section of the NDA	√			

Clinical Pharmacology Filing Form/Checklist for NDA 205787

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

	organized, indexed and paginated in a manner to allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	√			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			√	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	Submitted pediatric plan
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet	√			

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

	basic requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

This NDA is fileable from clinical pharmacology perspective. OSI inspection request for the pivotal relative BA study IJ-900DV-03O was sent on January 2nd, 2014. The requested action goal date is March 15, 2014.

If the NDA/BLA is not fileable from the clinical pharmacology 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.

There are no comments for sponsor at this time.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Background:

Kaleo Inc submitted a 505(b)(2) NDA 205787 for naloxone HCl auto-injector 0.4 mg (NAI) for IM or SC administration. (b) (4)

This NDA relies on the Agency's previous findings of safety and effectiveness for Narcan (NDA 016636). Since Narcan is discontinued, sponsor used a generic drug product (ANDA 72076) in the pivotal relative BA study IJ-900DV-03O. The to-be-marketed formulation was used in the relative BA study.

Study IJ-900DV-03O is randomized, single-dose, single-blind, two-sequence, two-period crossover BA, safety and tolerability study in healthy subjects. In this study, naloxone HCl delivered via NAI was demonstrated to have 15% higher C_{max} and comparable AUC values to the reference (naloxone HCl delivered via standard syringe).

Please find the filing slides for more details.

NDA 205787: EVZIO

Naloxone HCl Auto-Injector, 0.4 mg (NAI)

- **Sponsor:** Kaleo Inc
- Dosage form: single-use auto injector that delivers 0.4 mg naloxone HCl via SC or IM injection
- 505(b)(2) NDA
- Reference product:
 - Naloxone HCl Injection: ANDA 72076 to the RLD (NDA 016636, Narcan®, now discontinued), 1 mg/1 mL for IV, IM, and SC administration, available as 2 mL single dose disposable prefilled syringes

1

Proposed Labeling vs. Listed Drug

- Listed Drug
 - DOSAGE AND ADMINISTRATION:
 - Naloxone hydrochloride injection may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration, and it is recommended in emergency situations.
 - USAGE IN ADULTS: Narcotic Overdose – known or suspected
 - An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of narcotic-induced or partial narcotic-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.
- Evzio:
 - DOSAGE AND ADMINISTRATION:
 - Inject Evzio into the anterolateral aspect of the thigh, through clothing if necessary (NAI force testing results).
 - ...Upon actuation, Evzio automatically inserts the needle intramuscularly or subcutaneously, delivers 0.4 mg naloxone HCl injection, ...
 - USAGE IN ADULTS: Narcotic Overdose – known or suspected
 - An initial dose of 0.4 mg of naloxone hydrochloride may be administered intramuscularly or subcutaneously using Evzio. 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. If no response is observed after 10 mg of naloxone hydrochloride have been administered (including both Evzio and other naloxone hydrochloride products), the diagnosis of opioid-induced toxicity should be questioned.
- Clinical Pharmacology
 - Same as the reference product (Naloxone HCl injection from International Medication Systems, ANDA 72076)

2

Comparative BA Study IJ-900DV-03O

- Randomized, Single-Blind, Two-Sequence, Two-Period Crossover Comparative Bioavailability study, healthy (n = 30), PK, safety, and tolerability
 - *Test*: a single IM or SC injection of 0.4 mg naloxone HCl for injection USP using NAI
 - *Reference*: a single IM or SC injection of 0.4 mg naloxone HCl for injection USP using a standard syringe

3

Figure 2.7.1.2-1. Mean (\pm SD) Naloxone Plasma Concentration-Time Data

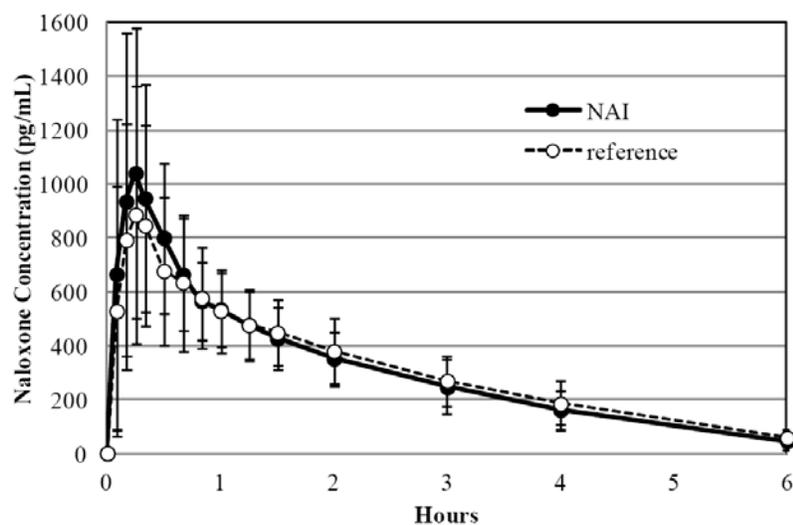


Table 2.7.1.2-1. Summary of Naloxone Plasma Pharmacokinetic Parameters and Comparative Bioavailability Results

Treatment	Statistic	C _{max} (pg/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _{0-t} (pg.h/mL)	AUC _{0-inf} (pg.h/mL)
Test IMP	Mean ± SD	1240 ± 638		1.28 ± 0.485	1830 ± 397	1930 ± 453
	%CV	51.4		38.0	21.7	23.4
	Median (Min-Max)	1070 (471-3110)	0.25 (0.08-1.23)	1.20 (0.885-3.13)	1790 (898-2680)	1910 (932-2960)
Reference IMP	Mean ± SD	1070 ± 482		1.36 ± 0.319	1850 ± 452	1980 ± 495
	%CV	45.1		23.5	24.4	25.0
	Median (Min-Max)	959 (294-2270)	0.33 (0.08-2.03)	1.28 (0.894-2.35)	1760 (859-3040)	1840 (922-3100)
	Treatment Ratio (Test/Reference)	1.15			0.993	0.983
	90% CI for Ratio	0.97, 1.37			0.94, 1.05	0.937, 1.03

Sources: JJ-900DV-03O Clinical Study Report Tables 14.2.3 and 14.2.4

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Recommendation

- Datasets for concentrations and PK parameters are included
- Filable from clin pharm perspective
- OSI inspection request for the relative BA study was sent on January 2nd, 2014. Requested action goal date is March 15, 2014.

6

Back up Slides

7

Previous Information Request

FDA Comment: Regarding your PK study IJ-900DV-03O, we did not find information on how many subjects received subcutaneous (SC) or intramuscular (IM) injection with either your product or the reference product, although you indicated in your study report that these products are given IM or SC.

Intelliject Response: There was no intention to determine whether the injection was into the subcutaneous (SC) space vs. intramuscular (IM) space. The injection process for the test (naloxone auto-injector) and reference products consisted of full insertion of the exposed needle length at a 90 degree angle to the injection site (into the mid-anterolateral thigh) prior to expulsion of the naloxone formulation through the needle into the tissue. The tissue layer location (i.e., subcutaneous (SC) space vs. intramuscular (IM) space) for the injection was dependent on the depth of fat under the skin and overlying the muscle and independent of the injection process.

FDA's Request is followed by Intelliject's response in bold:

1. Clarify how long each of the needles were and where we can find that information in the NDA.

The needle length for the reference product was 5/8" (see page 10 of the attached study manual: 209017 Intelliject IJ-900DV-03O SPM_15JAN2013.pdf).

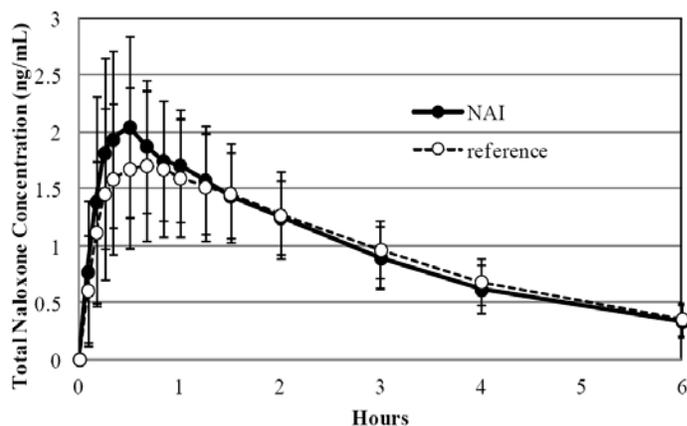
The exposed needle length for the test product (NAI) is a nominal 0.5" (NDA 205787 Sections 3.2.P.5.1 Specifications and 3.2.P.5.4 Batch Analyses).

2. Provide the location of the study manual in the NDA.

The study manual was not included in the NDA submission. A copy of the study manual is attached: 209017 Intelliject IJ-900DV-03O SPM_15JAN2013.pdf.

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Figure 2.7.1.2-2. Mean (\pm SD) Total Naloxone Plasma Concentration-Time Data



9

AUVI-Q Epinephrine Injection Auto-Injector (NDA 201739)

- Approved epinephrine reference product labeling (IM or SC into the anterolateral aspect of the thigh)
- Relative BA/BE Study
 - R, SD, SB, 2-Trt, CO study
 - Route of administration (either IM or SC)
- Approved AUVI-Q PI:
 - IM or SC into the anterolateral aspect of the thigh

10

Naloxone PK

- “Following parenteral administration, naloxone hydrochloride is rapidly distributed in the body.
- It is metabolized in the liver, primarily by glucuronide conjugation, and excreted in urine.
- In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes).
- In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours.”

11

Listed Drug PI: DOSAGE AND ADMINISTRATION

DOSAGE AND ADMINISTRATION

Naloxone hydrochloride injection may be administered [intravenously](#), [intramuscularly](#), or [subcutaneously](#). The most rapid onset of action is achieved by intravenous administration, and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of naloxone, the patient should be kept under continued surveillance and repeated doses of naloxone should be administered, as necessary.

Intravenous Infusion

Naloxone hydrochloride injection may be diluted for intravenous infusion in Sodium Chloride Injection 0.9% or Dextrose Injection 5%. The addition of 2 mg of naloxone in 500 mL of either solution provides a concentration of 0.004 mg/mL. Mixtures should be used within 24 hours. After 24 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient's response.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Naloxone hydrochloride injection should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high-molecular-weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to naloxone hydrochloride injection unless its effect on the chemical and physical stability of the solution has first been established.

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Listed Drug PI: USAGE IN ADULTS

USAGE IN ADULTS

Narcotic Overdose—Known or Suspected

An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of narcotic-induced or partial narcotic-induced toxicity should be questioned. [Intramuscular or subcutaneous](#) administration may be necessary if the intravenous route is not available.

Postoperative Narcotic Depression

For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of naloxone hydrochloride are usually sufficient. The dose of naloxone hydrochloride should be titrated according to the patient's response. Naloxone hydrochloride should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal— i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of naloxone may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating, or circulatory stress.

Repeat doses of naloxone may be required within one- to two-hour intervals depending upon the amount, type (i.e., short- or long-acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

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Listed Drug PI: USAGE IN CHILDREN AND NEONATES

USAGE IN CHILDREN

Narcotic Overdose—Known or Suspected

The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone may be administered [I.M. or S.C.](#) in divided doses. If necessary, naloxone hydrochloride injection can be diluted with sterile water for injection.

Postoperative Narcotic Depression

Follow the recommendations and cautions under "Adult Postoperative Depression." For the initial reversal of respiratory depression naloxone hydrochloride should be injected in increments of 0.005 mg to 0.01 mg intravenously at two- to three-minute intervals to the desired degree of reversal.

USAGE IN NEONATES

When using naloxone hydrochloride injection in Neonates a product containing 0.02 mg/mL should be used.

Narcotic-Induced Depression

The usual initial dose is 0.01 mg/kg body weight administered [I.V., I.M., or S.C.](#) This dose may be repeated in accordance with adult administration guidelines for postoperative narcotic depression.

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Proposed Evzio PI: DOSAGE AND ADMINISTRATION AND USAGE IN ADULTS

2 DOSAGE AND ADMINISTRATION

(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.

(b) (4)

(b) (4)

(b) (4)

15

FDA correspondence	Date	Question	Commitment / Request / Topic	Current Status
Pre-IND meeting Minutes	9/1/2011	15	Agreement to conduct a comparative bioavailability study.	No changes
Pre-IND meeting Minutes	9/1/2011	n/a	Clinical study bioavailability standard is relative bioavailability in lieu of strict bioequivalence.	No changes
Request for advice letter	5/24/2012	B1	FDA agreement with BA study objectives	No changes
Request for advice letter	5/24/2012	B2	FDA agreement with BA study design	No changes
Request for advice letter	5/24/2012	B3	FDA comment on power calculations. Recommends adding patients to account for possible additional variability	Increased number of patients in study in response to FDA advice. Study completed and report in preparation. Intellject Action Item: include results in the NDA.
Request for advice letter	5/24/2012	B4	FDA agreement on inclusion/exclusion criteria and recommendation for other exclusions.	No changes
Request for advice letter	5/24/2012	B5	FDA agreement on study treatments;	No changes
Request for advice letter	5/24/2012	B6	FDA agreement on clinical protocol assessments and evaluations	No changes
Request for advice letter	5/24/2012	B7	FDA agreement on statistical methods	No changes
Request for advice letter	5/24/2012	B8	No resolution: Question as to whether or not the clinical study would be adequate for NDA (FDA indicated it depends on the study results)	Intellject Action Item: include results in the NDA.
Request for advice letter	10/4/2012	B9	FDA agreement to reserve 24 dosing units as samples from the BA study	Clinical study site is storing 24 NAI and 60 reference product reserve samples.
Advice/Information letter	12/13/2012	1	Reminder to use final drug/device combination product in the clinical bioavailability study OR provide justification of changes and how the study results maintain relevance	Study completed pending final report. Action Item for NDA: Any changes to the product will be itemized in the NDA.

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

/s/

WEI QIU
01/13/2014

YUN XU
01/13/2014