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APPLICATION NUMBER:

205787Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Division / Office	DAAAP/ODE II
Reviewer Name(s)	Steven Galati M.D.
Review Completion Date	March 19, 2014
Established Name	Naloxone Injection
(Proposed) Trade Name	Evzio
Therapeutic Class	Opioid Antagonist
Applicant	Kaleo Inc.
Formulation(s)	Injection
Dosing Regimen	0.4 mg single-dose
Indication(s)	Opioid Overdose
Intended Population(s)	Out-of-Hospital Treatment of Opioid Overdose

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval with revisions to the proposed labeling.

1.2 Risk Benefit Assessment

This application is to support the product, Evzio [Naloxone Auto-Injector (NAI)], utilizing the 505(b)(2) pathway with the reference drug Narcan (NDA 016636). The product offers an out-of-hospital treatment option for patients who suffer from an opioid overdose. Given it would be unethical to evaluate a novel formulation/route of administration for naloxone in the setting of a clinical trial in patients with an opioid overdose when there are previously-approved formulations of naloxone available, the Applicant's required clinical program consisted of demonstrating comparable (or higher) pharmacokinetics in healthy volunteers in relation to an approved route of administration for naloxone in lieu of efficacy studies. In addition, based on the known safety profile and wide safety margin of naloxone, the greatest concern for treating the acutely life-threatening incident of an opioid overdose in any population is undertreating this potentially fatal event. The Applicant submitted the results of a pivotal comparative bioavailability trial (IJ-900DV-03O) and the results of this trial showed the reference product delivers naloxone at levels equal to (bioequivalent) or greater than the comparator. Therefore, the trial provided an adequate scientific bridge to the Agency's previous findings of safety and efficacy. Therefore, the Applicant may rely on the Agency's previous findings of safety and efficacy for Narcan as a 505(b)(2) application. Additional safety data was collected in the trial IJ-900DV-03O, and after review, no new safety signals were identified.

Naloxone is reserved mostly for use in the hospital setting for opioid overdose. This product provides a mechanism for treatment of opioid overdose in the outpatient setting, and to be administered by caregivers with or without medical training. In the outpatient setting, patients may intentionally or unintentionally overdose on opioids. Also, patients may accidentally ingest an opioid and require emergent treatment. Given these instances are medical emergencies; a treatment option that is effective in this environment may have a substantial impact on patient safety from a public health perspective. The Applicant proposed an indication [REDACTED] (b) (4) [REDACTED] discussed in more detail in Section 6.1. The Division is currently still reviewing the most appropriate indication for this drug product at the time of this review.

In addition to the pivotal comparative bioavailability trial, the Applicant also completed a Human Factors Engineering (HFE) development program to support approval of Evzio,

naloxone auto-injector (NAI). The device component was tested through the Applicant's human factors development program which included the following three studies:

- NAI Formative User Needs Study (IJ-1000FE-03O)
- NAI Formative Usability and Label Evaluation Study (IJ-1001FE-03O)
- Summative Design Validation Study of the User Interface (IJ-1025SE-03O)

The HFE provides additional supportive information in the final risk-benefit analysis of the product. These studies assist in an assessment of the drug-device's potential success in real world usage. A thorough review of the studies was performed by Quynh Nhu Nguyen, Biomedical Engineer/Human Factors Reviewer, dated October 2, 2013. The review stated "the consultant finds the human factors study acceptable, and no further optimization on the design and/or labeling is necessary."

Overall, the risk-benefit profile of the Evzio in this population, and treatment environment, is favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements are recommended at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Naloxone is a narcotic antagonist, a synthetic congener of oxymorphone.

The Applicant developed Evzio (NAI) as a combination drug-device product being submitted under Section 505(b)(2) of the Food, Drug, and Cosmetics Act (FD&C Act). Evzio is a single-use auto-injector that delivers 0.4 mg naloxone hydrochloride (HCl) via subcutaneous or intramuscular injection. Evzio is intended for patients who receive opioids out-of-the hospital and develop acute, opioid-related, central nervous system or respiratory depression. Evzio is designed for a caregiver or layperson to administer naloxone in the out-of-hospital setting for the treatment of an opioid overdose.

The Device Constituent Component of Evzio is a compact, user-actuated, (b) (4), auto-injection system.

2.2 Tables of Currently Available Treatments for Proposed Indications

Narcan (naloxone) was originally approved in 1971 intended for administration in patients who suffered harm from an opioid overdose or suspected overdose.

2.3 Availability of Proposed Active Ingredient in the United States

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

Table 1: Brand Name Naloxone Products and Indications

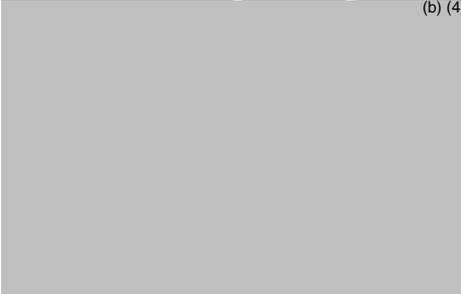
Drug Product Name	NDA	Approval Date	Dose Form	Indication
Narcan	016636	4/13/1971	Injection	Complete or partial reversal of opioid depression, including respiratory depression
Talwin NX (pentazocine/naloxone)	018733	12/06/1982	Tablet	Relief of moderate to severe pain
Suboxone (Buprenorphine/naloxone)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

2.4 Important Safety Issues With Consideration to Related Drugs

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2: Key Presubmission Regulatory Activity

Date	Meeting/ Submission Type	Key Comments
7/02/2011	Type B Meeting (pre-IND)	<ul style="list-style-type: none"> • EVZIO will be regulated as a drug/device combination product • 505(b)(2) pathway appropriate • A relative bioavailability or bioequivalence study with listed product required to demonstrate pharmacokinetic (PK) comparability • Efficacy and safety based on comparability of PK data • Considering naloxone has a relatively large therapeutic index window, the concern would be greater if EVZIO delivers less drug
1/8/2013	Memorandum to File	<ul style="list-style-type: none"> • Fast Track designation granted •  (b) (4)
6/4/2013	Type B Meeting (pre-NDA)	<ul style="list-style-type: none"> • Division agreed the NDA may be submitted as a rolling submission • Addition of “ (b) (4)” proposed in labeling required defining • EVZIO is subject to PREA
7/19/2013	Initial submission to rolling review	<ul style="list-style-type: none"> • Pivotal PK study • Clinical overview and summary
10/29/2013	Draft labeling submitted	
11/6/2013	Teleconference with Applicant	<ul style="list-style-type: none"> • Discussed appropriateness of product’s indication • Determined that definition of

Date	Meeting/ Submission Type	Key Comments
		targeted population as “ (b) (4) ” is difficult to define and potentially may limit populations who would benefit from the drug-device Discussed alternative language for the indication section of the drug labeling
12/11/2013	Updated draft labeling submitted	
12/16/2013	Ownership transferred from Intelliject to Kaleo Inc	
12/20/2013 – PDUFA start date	Final portions of NDA submitted to the NDA	<ul style="list-style-type: none"> • Pediatric study plan • Quality systems information • Description of automated assembly process
3/17/14	Literature review and analysis of safety data for the adverse events section of the product labeling	<ul style="list-style-type: none"> • Summary of safety for Section 6 of product labeling

2.6 Other Relevant Background Information

There is no additional information to be discussed in this section.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

All data and documents in this application were electronically submitted following the guidances for electronic submission. The documents were organized in electronic Common Technical Document (eCTD) format. The datasets were not in Study Data Tabulation Model (SDTM) format. The overall quality of the submission was adequate. The organization and the ability to navigate the NDA were acceptable.

3.2 Compliance with Good Clinical Practices

The Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with the United States Food and Drug Administration regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations Parts 50, 56, and 312. The Applicant also states that the studies were approved by Institutional Review

Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

3.3 Financial Disclosures

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator", certifying that they had no financial interests or arrangements to disclose (see Appendix for Clinical Investigator Financial Disclosure). A total of six investigators were listed and the study was performed through the contract research organization, Parexel International Early Phase Clinical Unit-Baltimore.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

There was no clinically relevant data for the following disciplines: chemistry, manufacturing and controls, clinical microbiology, preclinical and pharmacology/toxicology review disciplines.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Naloxone is an opioid antagonist, a synthetic congener of oxymorphone.

4.4.2 Pharmacodynamics

When naloxone hydrochloride is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly.

4.4.3 Pharmacokinetics

Overall, the bioavailability is comparable between the between the two delivery systems; Evzio (0.5 inch needle) and standard syringe (5/8 of an inch needle). For both area under the curve (AUC) parameters, naloxone administered from Evzio is bioequivalent to naloxone administered from the standard syringe (Table 3). The C_{max} is similar, but not bioequivalent to the reference test. Table 3 shows the geometric mean ratio was 1.15 with a 90% CI of (0.97, 1.37). The C_{max} is slightly higher for the naloxone delivered through the Evzio, however, this should not relate to any safety concern given the therapeutic safety margin for naloxone and is consistent with the

Division's requirements. See Dr. Wei Qiu's full report for full details of the study results and design.

Table 3: 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-t} (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; HCl = Hydrochloride; USP = United States Pharmacopeia

Data source: Section 14.2, Table 14.2.4

Source: Clinical study report p. 60

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The studies conducted in support of this NDA for Evzio are listed below (Table 4).

Table 4: Clinical Studies Submitted in Support of this Application

Clinical Trial	Population	Number of Subjects	Relevance
<i>Pivotal Comparative Bioavailability Study</i>			
IJ-900DV-03O	Healthy volunteers	N = 30	Pivotal comparative bioavailability trial to support efficacy and safety of this application.
<i>Human Factors Studies</i>			
IJ-1000FE-03O	Caregivers caring for individual taking opioid	N = 9 caregivers	Formative study to optimize NAI interface (user needs study)

Clinical Trial	Population	Number of Subjects	Relevance
	medication		
IJ-1001FE-03O	Patients taking opioids and caregivers caring for individual taking opioid medication	N = 7 patients and 7 caregivers	Formative study to evaluate NAI and various labeling designs and instructions for use
IJ-1025SE-03O	Untrained volunteers	N = 40 (20 Juveniles, aged 12-19, and 20 Adults, aged 20-65)	Summative design validation study of the user interface Results showed majority of untrained users could effectively administer naloxone

Source: Derived from Applicant's submission, NDA 205787

As described in Section 1.2, the pivotal comparative bioavailability study was the only required clinical study. The PK parameters were found to either bioequivalent (AUC) or greater (Cmax) than the comparator naloxone administered via a standard syringe and described in Section 4.4.3, Clinical Pharmacology. Therefore the Applicant was able to rely on the Agency's previous findings of safety and efficacy for the reference product Narcan.

The device component was tested through the Applicant's human factors development program which included three of the studies listed in Table 4. These studies assist in an assessment of the drug-device's potential success in real world usage. A thorough review of the studies was performed by Quynh Nhu Nguyen, Biomedical Engineer/Human Factors Reviewer, dated October 2, 2013.

5.2 Review Strategy

IJ-1000FE-03O is the pivotal comparative bioavailability trial which provided a scientific bridge to the Agency's previous findings of safety and effectiveness for Narcan, for this 505(b)(2) NDA. As described in Section 1.2, for ethical reasons of studying novel drug products in life-threatening situations, such as an opioid overdose when approved treatment exists, the Applicant's clinical program consisted of demonstrating comparable (or higher) pharmacokinetics in healthy volunteers in relation to an approved route of administration for naloxone in lieu of efficacy studies. Given the wide safety margin of naloxone, the concern would be undertreating an opioid overdose. A brief description of the design of IJ-1000FE-03O is discussed in Section 5.3, Discussion of Individual Studies/Clinical Trials. In the description of the trial, Evzio will be referred to as NAI given the protocol predated the proposed tradename. Detailed information regarding the design and findings are discussed by Dr. Wei Qiu, clinical pharmacologist.

5.3 Discussion of Individual Studies/Clinical Trials

Trial IJ-1000FE-03O

“A Randomized, Single-Blind, Two-Sequence, Two-Period Comparative Bioavailability Study of Two Naloxone Hydrochloride Products in Healthy Human Volunteers”

Conducted from January 8, 2013 to February 26, 2013

One clinical site in Baltimore, MD

Protocol

Objective/Rationale

Primary: 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

Secondary: To assess the safety and tolerability of naloxone injection by NAI compared to standard syringe.

Overall Design

This was to be a Phase 1, randomized, single-blind, single-dose, two-sequence, two-period crossover bioavailability, safety and tolerability study in 30 healthy male and female subjects to evaluate the PK of 0.4 mg of naloxone administered by injection using either NAI or a standard syringe. The study consisted of a several week screening period and a 3 day inpatient admission to complete both dosing periods. Safety assessments were conducted throughout the study, including physical examinations (PE), pregnancy tests, routine clinical laboratory assessments (chemistry, hematology, urinalysis), ECGs, adverse event (AE) assessments, vital sign assessments and evaluation of the injection site.

Treatment

Each subject was to receive two doses of 0.4 mg of naloxone, either through NAI (0.5 inch needle) or a standard syringe (5/8 of an inch needle) on Day 1 and the alternate on Day 2.

Population and Procedures

Planned enrollment was to be 30 healthy subjects. Subjects were randomized to receive either method of injection and then crossover to the alternate method on Day 2.

Inclusion Criteria

- Male or female ≥ 18 and ≤ 45 years of age
- Able to provide written informed consent

- Willing and able to participate in all required study activities
- Body mass index (BMI) between 18.5 and 29.9 kg/m², inclusive and a weight ≥50 kg and ≤100 kg
- If female and of childbearing potential, must have had negative pregnancy tests at screening and Day -1 (admission) and must have been using highly effective contraception¹ and committed to continue its use for 28 days after final naloxone administration
- 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 naloxone administration
- No clinically significant abnormal findings on PE, medical history, ECG or clinical lab results during screening or admission
- Vital signs were within clinically acceptable ranges at screening and admission

Exclusion Criteria

- Clinically significant medical conditions²
- Diabetes Mellitus or cardiac risk factors³ or the prior use of potentially cardiotoxic drugs
- History of allergic or adverse responses to naloxone
- History of unusual bruising or prolonged bleeding
- Consumption of xanthines during the 24 hours preceding Day –1 (admission) or during the study
- Blood donation within 56 days or plasma donation within 14 days of admission
- Participation in a clinical trial within 30 days of admission
- Use of any over-the-counter (OTC) or prescription medication or grapefruit within 14 days admission or during the study⁴
- Use of any enzyme altering drug (e.g., barbiturates, phenothiazines, cimetidine, carbamazepine) within 30 days before admission or during study
- Smoking or use of tobacco products within 6 months of admission or during study⁵

¹ Established, consistent use of oral, injected or implanted hormonal methods of contraception established for at least 90 days before admission. Examples included 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.

² Gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric or cardiovascular disease or any other condition which, that in the opinion of the investigator, would compromise the safety of the subject or impacted the validity of the results

³ Examples include family history, hypertension, hypercholesterolemia

⁴ Exception is acetaminophen under 1 gram per day and use of OTC contraceptive products

⁵ Determined by a urine cotinine concentration >200 ng/mL

- Females trying to conceive, donated ova, were pregnant, or were lactating or breast feeding at screening or throughout study
- Males who donated sperm at screening or throughout the study
- Positive serum pregnancy test at Screening or admission (Day -1)
- Positive blood screen for HIV, HBV, or HCV
- Positive urine screen for drugs-of-abuse or breath alcohol test at screening or admission
- Alcohol use within 72 hours of admission
- History of any substance abuse within 6 months prior to admission

Procedures

The study was to consist of a screening period and a 3-day, inpatient treatment period. The subjects were to receive the study medication after eligibility confirmed and randomized to receive either NAI or a standard syringe on Day 1, then crossover to the alternate treatment on Day 2. There was to be a 24 hour washout period between doses. PK assessments were to be collected for each dosing period. After subjects were to receive a second dose of naloxone, additional safety assessments were to be completed prior to discharge from the unit.

Subject Withdrawal

Subjects were to be free to withdraw from participation in this study at any time and for any reason. Subjects who experienced an AE were to be followed until the AE resolved or until 30 days from the end of the study.

Evaluations/Endpoints

The primary objective of this study was to compare the PK parameters of naloxone administered from NAI and a standard syringe. Subjects were to have PK assessments (C_{max} , T_{max} , AUC parameters) 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.

Safety Assessments

- Incidence of TEAEs throughout study period
- Vital sign measurements⁶
- Physical examination (screening, admission or Day -1 and Day 2)⁷
- Laboratory tests(screening, admission or Day -1 and Day 2):
 - Chemistry
 - Hematology

⁶ Blood pressure, pulse, respiratory rate and body temperature were to be collected at screening, admission, 60 minutes pre-dose and approximately 6 hours post-dose and were taken in the supine position after resting for ≥ 5 minutes, and before discharge

⁷ Includes inspection of the injection sites between 5 minutes pre-dose and immediately prior to dosing and between 60 and 120 minutes post-dose on each dosing day and at end-of-study

- Urinalysis
- ECGs⁸

Results

Subject Overview

A total of 30 subjects were screened met all the eligibility criteria and were subsequently randomized in the study. All the subjects completed the study and were included in both the PK and safety analyses.

Subject Disposition

All 30 subjects that were randomized completed the study.

Demographics

The demographic characteristics are displayed in Table 5. The population was diverse, consisting of Black or African American, White, Hispanic or Latino, Native Hawaiian or other Pacific Islander males and females with ages ranging from 20 to 43 years of age. The trial population was predominantly female (18 subjects [60%]) and Black or African American (20 subjects [66.7%]). The mean body mass index (BMI) was 24.91 kg/m², ranging from 20 to 29.8 m/kg². Given the Applicant is relying on the agency's previous findings of safety for Narcan, this appears to be an appropriate population for this PK trial.

⁸ Performed at screening, admission, and after collection of final blood sample for PK analysis

Table 5: Summary of Demographic Parameters (Study IJ-900DV-030)

Variable	n	Mean or Percentage*	Minimum	Maximum
Age (years)	30	30.8	20	43
Height (cm)	30	170.6	159	193
Weight (kg)	30	72.76	51.1	96.2
BMI (kg/m ²)	30	24.91	20.0	29.8
Gender: Female	18	60.0%		
Gender: Male	12	40.0%		
Race: White	9	30.0%		
Race: Native Hawaiian or other Pacific Islander	1	3.3%		
Race: Black/African American	20	66.7%		
Ethnicity: Hispanic/Latino	5	16.7%		
Ethnicity: Non-Hispanic/Latino	25	83.3%		

n = number of subjects; BMI = Body mass index

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

Data source: IJ-900DV-030 CSR [Tables 14.1.2](#) and [14.1.3](#)

Source: Applicant's Clinical Summary p. 21

Protocol Violations

The protocol deviations consisted of non-significant events (e.g., pre-dose injection site examine 1 minute early, fasting requirements deviated by 1- 37 minutes in several subjects) and should not impact the study results.

Dosing Information

The planned dosing consisted of two, single doses of 0.4 mg of naloxone separated by 24 hours. The exposed needle length for the test product (NAI) was a nominal 0.5 inches and 5/8 of an inch for the reference product. Naloxone was delivered either subcutaneously or intramuscularly depending on the amount of subcutaneous tissue present in a particular subject.

Safety Findings

A brief summary of the safety findings for this clinical trial is provided herein. A complete discussion of safety can be found in Section 7.

Deaths

No subjects died during the trial.

Serious Adverse Events (SAEs)

No SAEs occurred during the trial.

Discontinuations Due to Adverse Events

No subject discontinued due to an AE during the trial.

6 Review of Efficacy

Efficacy Summary

The Applicant utilized the 505(b)(2) pathway, relying on the Agency's previous efficacy and safety findings for the naloxone product, Narcan (NDA016636), and bridged to those previous findings by performing a successful comparative bioavailability study. An efficacy study is not required by the Division for the following reasons. It would be unethical to administer a novel formulation/route of administration for naloxone to patients with an opioid overdose in the setting of a clinical trial when there are already-approved formulations of naloxone available. Therefore, as discussed in the pre-IND meeting, the Applicant's clinical program consisted of demonstrating comparable (or higher) pharmacokinetics in healthy volunteers in relation to an approved route of administration for naloxone in lieu of efficacy studies. The Division agreed this could be accomplished through a successful, single, pivotal, comparative bioavailability trial. Based on the review of the pivotal comparative bioavailability trial, IJ-1000FE-030, naloxone delivered by the Evzio and the standard syringe, delivered via the SC or IM route, showed comparable pharmacokinetics and met the requirements set forth by the Division (Table 3). Therefore, the Applicant may rely on the Agency's previous findings of safety and efficacy for the Narcan.

Deleted sections:

6.1.4 Analysis of Primary Endpoint(s); 6.1.5 Analysis of Secondary Endpoints(s); 6.1.6 Other Endpoints; 6.1.7 Subpopulations; 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations; 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects; and 6.1.10 Additional Efficacy Issues/Analyses were all deleted since the Division did not require the Applicant to conduct efficacy studies.

6.1 Indication

The Applicant proposed the following language within their product's prescribing information:

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

The Division does not agree with the Applicant's proposed language for the proposed indication as it does not necessarily reflect the intended target population [REDACTED] (b) (4)

[REDACTED] Furthermore, the Division recognizes the importance of this product in addressing a major public health crisis and would not want to unintentionally limit its use. Product labeling discussions are currently ongoing at the time of the report's completion. However, below is proposed new language for the indication to be included in the product labeling.

- EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
- EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present.
- EVZIO is not a substitute for immediate medical care.

I believe this language better represents the indication for the intended target population and addresses the two concerns identified above.

6.1.1 Methods

See Section 5.3.

6.1.2 Demographics

See Section 5.3.

6.1.3 Subject Disposition

See Section 5.3.

7 Review of Safety

Safety Summary

The Applicant submitted a 505(b)(2) application referencing the approved drug, Narcan (NDA 016636), to support the clinical efficacy and safety of Evzio in the treatment of opioid related overdose. As previously described in Section 1.2 and Section 6, the Division agreed with the Applicant's plan to submit data from a PK study in lieu of efficacy and safety studies if the PK parameters (i.e., AUC and C_{max}) were found to be bioequivalent or show greater values. The PK data was found to be bioequivalent or greater as described in Section 4.4 and shown in Table 3. Therefore, the Applicant may rely on the Agency's previous findings of safety and efficacy for Narcan (NDA 016636) for this application. Additional safety data was collected from the pivotal comparative bioavailability trial (IJ-900DV-03O) and discussed below. Overall, the safety data from trial IJ-900DV-03O did not show any new safety signals. There were no deaths, serious adverse events (SAE) or withdrawals.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The pivotal comparative bioavailability trial (IJ-900DV-03O) consisted of 30 healthy adult subjects aged 18-45 years of age. The safety data discussed below are from trial IJ-900DV-03O and provide additional support to the Agency's previous findings of safety for the reference drug Narcan. The entire 30 subjects were included in the safety group. As described in Section 4.4.3, the trial showed the AUC parameters were bioequivalent between both naloxone delivery systems. The C_{max} is slightly higher for the naloxone delivered through the Evzio, however, this should not relate to any safety concern given the wide therapeutic safety margin for naloxone. Given this application is a 505(b)(2), and the results of trial IJ-900DV-03O showed naloxone used in Evzio were comparable to the reference drug, the Agency's previous findings of safety for the reference product Narcan (NDA 016636) may be relied upon for this application. A number of subsections below are not relevant and reference to the deleted sections is listed below. The Applicant also performed an analysis of the literature to support the safety of Evzio. Literature references are briefly discussed in Section 7.7.

Deleted Sections

- 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence. This section was not relevant to this application because there was no relevant data to be pooled.
- 7.2.2 Explorations for Dose Response. This section was not relevant since only a single dose was studied and this product is designed to be a single-fixed dose product
- 7.2.3 Special Animal and/or In Vitro Testing. No data was submitted to inform a discussion for this section.
- 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class. No data was submitted to inform a discussion for this section.
- 7.4.6 Immunogenicity was deleted because no data was submitted to inform a discussion for this section.
- 7.5.3 Drug-Demographic Interactions, 7.5.4 Drug-Disease Interactions, 7.5.5 Drug-Drug Interactions, and 7.6.1 Human Carcinogenicity were all deleted. No data was submitted to inform a discussion for this section.
- 7.5.2 Time Dependency for Adverse Events. This trial only includes a single dose of medication, therefore, this section was irrelevant.
- 7.2.5 Metabolic, Clearance, and Interaction Workup. This section was deleted because only a comparative PK trial was required and the Applicant could rely on the Agency's previous findings for Narcan.
- 7.3.5 Submission Specific Primary Safety Concerns. This section was deleted because there were no specific primary safety concerns in this PK study.
- 7.5 Other Safety Explorations. This section is not relevant given the drug was only given as a single, fixed-dose in the trial.
- 7.6 Human Reproduction and Pregnancy Data. This section was deleted because no new data was submitted for an analysis.

7.1.2 Categorization of Adverse Events

All treatment emergent adverse events (TEAEs) were coded by using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1. If the same AE (using the MedDRA Preferred Term) was reported more than once for the same subject within a dosing period, it was to only appear once for that specified treatment. For subjects with multiple AEs within a dosing period of the same MedDRA Preferred Term and of different severities, the AE with the highest assessment of severity was used for that dosing period. Adverse events that emerged in one dosing period and carried over into the next period were attributed to only the period in which the AE emerged.

7.2 Adequacy of Safety Assessments

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

Exposure

Thirty subjects received naloxone in study IJ-DV900-03O, and all the subjects received both the investigational medicinal product (Evzio/NAI - naloxone 0.4 mg) and reference product (naloxone 0.4 mg via syringe). Because the Applicant is utilizing the 505(b)(2) pathway and relying on the Agency's previous findings of Narcan, the exposure to 30 subjects is adequate for the purposes of this safety evaluation.

Demographics

Demographics are discussed in Section 5.3.

7.2.4 Routine Clinical Testing

The safety monitoring plan is outlined for the pivotal trial in Section 5.3, which appears adequate for this population.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in this trial.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAE).

7.3.3 Dropouts and/or Discontinuations

There were no dropouts or discontinuations in the study.

7.3.4 Significant Adverse Events

All of the TEAEs were of mild intensity and no notable differences between the test groups. There were no marked laboratory abnormalities, and no events led to

substantial intervention. I also reviewed the submitted ECG data for all subjects and found no relevant changes between test groups.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant defined the safety population as all subjects who received at least one dose of study drug. No adverse event was reported by more than 2 subjects in the pivotal study IJ-900DV-03O. Dizziness (n=2) was the most common event associated with the test drug (Table 6). No subject experienced a TEAE that resulted in their withdrawal from the trial. Overall, there are no newly identified safety signals. I reviewed the Applicant’s dataset and found no substantial differences that would affect my perception of the adverse event profile.

Table 6: Summary of All Treatment-Emergent Adverse Events (Study IJ-900DV-03O)

System Organ Class Preferred Term	Treatment	
	Test IMP N = 30 n (%)	Reference IMP N = 30 n (%)
Gastrointestinal Disorders	1 (3.3%)	1 (3.3%)
Nausea	1 (3.3%)	1 (3.3%)
General Disorders and Administration Site Conditions	1 (3.3%)	1 (3.3%)
Injection Site Pain	0 (0.0%)	1 (3.3%)
Vessel Puncture Site Haematoma	1 (3.3%)	0 (0.0%)
Nervous System Disorders	3 (10.0%)	3 (10.0%)
Anosmia	1 (3.3%)	0 (0.0%)
Dizziness	2 (6.7%)	0 (0.0%)
Dysgeusia	1 (3.3%)	0 (0.0%)
Headache	0 (0.0%)	2 (6.7%)
Presyncope	0 (0.0%)	1 (3.3%)
Skin And Subcutaneous Tissue Disorders	1 (3.3%)	0 (0.0%)
Hyperhidrosis	1 (3.3%)	0 (0.0%)

N = number of subjects exposed to treatment; n = number of subjects

Data source: IJ-900DV-03O CSR [Table 14.3.1.2](#)

Source: Clinical Summary – Summary of Clinical Safety p. 22

7.4.2 Laboratory Findings

In Study IJ-900DV-03O, no clinically significant findings were noted for any clinical chemistry, hematology or urinalysis results in either group. I reviewed through the data tables provided by the Applicant and did not identify any clinically relevant laboratory findings.

7.4.3 Vital Signs

There were no observable treatment-related trend in vital sign parameters and median absolute values were similar for both groups. No TEAEs were related to vital sign measurements.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed on each subject at screening, Day -1, and Day 2 (6 hours post dose). I reviewed the combined and individual ECG data submitted by the Applicant, and none of the abnormalities appeared to be clinically relevant. No subject developed a prolonged QTcF and the mean QTcF was not increased. The PR interval did not show any significant changes from the subject's baseline values. Several subjects developed a heart rate slightly out of the normal range (e.g., subject 117 heart rate was 49, 52, and 57). This likely represents a subject's normal range and not related to the study drug.

7.4.5 Special Safety Studies/Clinical Trials

No special safety trials were included in this application. The prescribing information describes several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema in post-operative patients. Many of these patients had pre-existing cardiovascular disorders or received a drug(s) which may affect the cardiovascular system. This information is not particularly relevant to Evzio given the product is proposed for out-of-hospital use.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Division outlined the requirements for the Applicant's pediatric plan during the pre-NDA meeting (June 4, 2013). The Applicant proposed a single-dose regimen of 0.4 mg. However, the current labeling for Narcan provides separate dosing and administration regimens for adults and children, including a weight-based dosing regimen. The Division stated the new dosing regimen triggered the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), and the Applicant is required to provide an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Also, the Applicant was informed if they believe a waiver for any pediatric age group is appropriate, they must

(b) (4)

Although the product will be prescribed to a patient taking opioids out of the hospital, the product may also be used for anyone, including children, who may be exposed to opioids. The concern for the pediatric age range includes a number of situations including, but not limited to the following: accidental use or ingestion, intentional misuse, and exposure to duragesic patches. Similarly to the adult population, there is a wide safety margin for naloxone, and the clinical consequences of not treating an opioid overdose are grave, and it is not practical to deliver pediatric weight-based dosing for naloxone (as is currently recommended in the Narcan labeling) in a community setting. The benefit of a potentially life-saving drug product with a wide safety margin considerably outweighs the risk of not treating an opioid overdose which may result in death. Therefore, the risk/benefit ratio convincingly demonstrates support for labeling the proposed product containing a 0.4 mg fixed dose of naloxone for all pediatric age ranges.

There are several concerns about the product's use in pediatric population, especially the very young age groups. Given there is some force needed to administer the drug, there is the potential for the needle to strike bone and potentially break off within the subcutaneous or muscle tissue and possibly not deliver the dose. The Applicant submitted information justifying the safety of the exposed needle length of 0.5 inches on 2/18/2014. The safety concern is whether this needle length may over penetrate the intramuscular space leading to the needle striking bone, especially in the younger pediatric population who possess less subcutaneous tissue. The Applicant submitted the Center for Disease Control (CDC) recommendations based on intramuscular injection of vaccines. The CDC recommends 5/8" needle length for intramuscular injections, based on injection of vaccines, into the anterolateral thigh muscle in the newborn (0-28 days old) age group. The Applicant also submitted a literature reference which examined the safety of needle lengths injected into the subcutaneous fat and muscle in 100 children aged 0 – 6 years old relative to the CDC recommended needle lengths for vaccinations requiring intramuscular injection. The reference stated a 7/8 inch needle would result in 4% over penetration within this age group. Therefore, the shorter exposed needle length or 0.5 inches, such as the one for Evzio, should result in substantially less than 4% over penetration in this population; however, Evzio may require additional force compared to vaccine administration resulting in compression of the soft tissue layer. Based on the CDC recommendations for needle length, the literature reference, and the likely rare event of requiring Evzio in a newborn and the needle breaking off, as well as the risk/benefit of the clinical scenario, I believe the potentially life-saving benefit far outweighs the risk of these events.

However, I do recommend routine postmarketing surveillance, and if a signal arises, the Applicant may need to perform additional safety studies and adjust the language in the product labeling. At the current time, I recommend language be included within the product labeling for this young, vulnerable age group (i.e., age less than 1 year old). For example, recommendations may include a follow-up inspection of the injection site by a health professional or an x-ray to assess for needle fragments. The Pediatric and Maternal Health Service (PMHS) has been consulted and will assist in the pediatric labeling section prior to approval.

The above information was discussed with the Pediatric Review Committee (PeRC) on 3/5/2014, and the committee was in agreement with the Division on the above discussion.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no instances of overdose in the pivotal comparative bioavailability study IJ-900DV-030. The currently approved Narcan product labeling states there is no clinical experience with naloxone overdosage in humans. The Applicant referenced literature which concluded high doses of naloxone have been administered in clinical trials with minimal toxicity. Naloxone does not have any known abuse potential since it does not produce subjective effects or physical dependence and precipitates abstinence in morphine-dependent subject. There is no data available regarding withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

No additional safety studies or updates were submitted for review.

8 Postmarket Experience

Although Evzio includes a device component, there is considerable experience with naloxone and published literature to support its safety and effectiveness. A brief review of the literature submitted by the Applicant is described in Section 9.1.

9 Appendices

9.1 Literature Review/References

The Applicant submitted an analysis of a PubMed database search for published data relevant to the safety and efficacy of naloxone through June 9, 2013. The analysis of the literature supports the safety and effectiveness of naloxone for the treatment of respiratory depression secondary to opioid overdose. Naloxone is the standard of care,

with no absolute contraindications, for the treatment of opioid-related respiratory depression regardless of age, sex or ethnicity. Cardiovascular events, pulmonary edema, and seizures have been reported and studied in the literature. However, separating the effects of naloxone from the effects of concomitant medications and pre-existing disorders has been problematic. High doses of naloxone have been administered in clinical trials and generally have been well tolerated. Overall, naloxone is considered to have a wide safety margin even at doses higher than the proposed fixed dose of 0.4 mg. Review of the provided literature reveals no new safety signals that would alter the risk-benefit profile of Evzio in this population.

An additional submission was submitted 3/17/14 which included an analysis of the literature, in combination with the safety data collected from the pivotal pharmacokinetic trial (IJ-DV900-030) for this application, to be included in Section 6 of the product labeling. The safety profile of naloxone in the literature is biased towards settings of use in opioid withdrawal. The Division requested the Applicant attempt to characterize the safety of naloxone based on the drug and not the effects of opioid withdrawal. The Applicant provided a summary of their findings and proposed language for Section 6 of the product labeling. The Applicant based the language for Sections 6 by combining AEs associated with naloxone use in opioid naïve subjects in the literature and possibly related AEs reported in the clinical trial IJ-900DV-030. I agree that the literature is sparse regarding characterizing the direct AEs caused by naloxone and not a consequence of opioid withdrawal. The Applicant's proposal appears reasonable.

Cardiac Disorders

- palpitations

Gastrointestinal Disorders

- nausea, vomiting, dyspepsia

Nervous System Disorders

- tremor, dystonia, dizziness, headache, drowsiness (sedation), yawning

Psychiatric Disorders

- agitation, anxiety, anger, confusion, dysphoria, dysesthesia

Skin and Integumentary Disorders

- injection site reaction, diaphoresis (hyperhidrosis and sweating)

Vascular Disorders

- pallor, flushing

Details of the frequency of the AEs were not reported in all the literature and could not be estimated. After a review of the literature submitted and my own review of PubMed, the literature is sparse regarding the AEs that may be directly linked to naloxone, excluding opioid withdrawal symptoms and post-operative events.

9.2 Labeling Recommendations

Product labeling is still under review at the completion of this report. However, labeling recommendations are included within the relevant sections of this report.

9.3 Advisory Committee Meeting

There was no advisory committee for this drug product.

APPENDIX 9.4 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: 205787

Submission Date(s): December 20, 2013

Applicant: Kaleo INC.

Product: Evzio (naloxone auto-injector)

Reviewer: Steven Galati

Date of Review: March 19, 2014

Covered Clinical Study (Name and/or Number): IJ-1000FE-03O

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>6</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None identified</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None identified</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>N/A</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

The Applicant submitted Form FDA 3454 “Certification: Financial Interests and Arrangements of Clinical Investigator”, and stated a total of six investigators were listed and the study was performed through the contract research organization, Parexel International Early Phase Clinical Unit-Baltimore. The form certified that they had no financial interests or arrangements to disclose.

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Given no investigator had financial interests or arrangements to disclose, the possibility of bias in the results based on financial interests is unlikely.

¹ See [web address].

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

/s/

STEVEN A GALATI
03/19/2014

JOSHUA M LLOYD
03/19/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205787

Applicant: Kaleo INC

Stamp Date: 12/20/13

Drug Name: Naloxone Auto-injector

NDA/BLA Type: Priority/Fast Track

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?		X		Applicant submitted integrated summary information in the clinical summary and clinical overview, and this is acceptable for filing. We will request the Applicant to submit a cross-reference to this information in the ISS
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		Applicant submitted integrated summary information in the clinical summary and clinical overview, and this is acceptable for filing. We will request the Applicant to submit a cross-reference to this information in the ISE
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	Not a chronic indication.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			The Division required a pivotal relative BA study between the proposed product and the reference product, to support this application, and the Applicant collected safety data in this study.
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	There were no deaths, discontinuations, or SAEs in the pivotal PK study
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	None required. There were no deaths, discontinuations, or SAEs in the pivotal PK study.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____

If the Application is not fileable from the clinical 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.

1. We note that you have submitted integrated summary information (i.e., efficacy and safety) in the clinical overview and clinical summary. However, you must cross-reference this information in Module 5.3.5.3 (i.e., the integrated summary of safety [ISS] and integrated summary of effectiveness [ISE]).

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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

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

/s/

STEVEN A GALATI
01/10/2014

JOSHUA M LLOYD
01/10/2014