

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209862Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 205787 (Supplement 7)

Supporting document/s: SDNs 187, 201, and 203 (Electronic Document Room Sequence Numbers 80, 94, and 96)

Applicant's letter date: April 19, 2016 (SDN 187), July 1, 2016 (SDN 201), and July 15, 2016 (SDN 203)

CDER stamp date: April 19, 2016 (SDN 187), July 1, 2016 (SDN 201), and July 15, 2016 (SDN 203)

Product: EVZIO (naloxone hydrochloride) auto-injector

Indication: For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, and for immediate administration as emergency therapy in settings where opioids may be present

Applicant: Kaleo Inc.

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

Reviewer: Carlic K. Huynh, PhD

Team Leader: Elizabeth A. Bolan, PhD

Supervisor: R. Daniel Mellon, PhD

Division Director: Sharon Hertz, MD

Project Manager: Diana Walker

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205787 are owned by Kaleo Inc. or are data for which Kaleo Inc. has obtained a written right of reference.

Any information or data necessary for approval of NDA 205787 that Kaleo Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205787.

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY.....	4
1.1	INTRODUCTION	4
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	4
1.3	RECOMMENDATIONS	4
2	DRUG INFORMATION.....	8
2.1	DRUG	8
2.2	RELEVANT INDS, NDAs, BLAs AND DMFs.....	9
2.3	DRUG FORMULATION	10
2.4	COMMENTS ON NOVEL EXCIPIENTS	10
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	10
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN.....	13
2.7	REGULATORY BACKGROUND	14
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	14

1 Executive Summary

1.1 Introduction

The Applicant, Kaleo Inc., originally submitted a New Drug Application for EVZIO naloxone hydrochloride auto-injector, 0.4 mg and was approved on April 3, 2014. This is a supplemental application for the addition of a 2.0 mg dose of naloxone HCl.

This review will focus on the drug substance and drug product specifications as well as the container closure for the proposed EVZIO naloxone hydrochloride auto-injector 2.0 mg product and any differences with the approved EVZIO naloxone hydrochloride auto-injector 0.4 mg product. The supplement also includes revised labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR). Reference is made to the original nonclinical review, which was written by Dr. Carlic K. Huynh and dated March 20, 2014.

1.2 Brief Discussion of Nonclinical Findings

There were no nonclinical studies submitted in this NDA. The formulation is identical to the approved 0.4 mg dosage strength formulation with the exception of 2 mg of naloxone hydrochloride in this submission. The drug substance and drug product specifications are identical to the approved 0.4 mg dosage strength product. The container closure is identical to the approved 0.4 mg dosage strength product, the extractable assessment was done appropriately with harsh solvents, and the leachable profile is not different than the currently approved drug product formulation. (b) (4) is present as a leachable; however, the levels do not represent a nonclinical safety concern. Moreover, the proposed product is for a life-saving indication. Therefore, there are no additional nonclinical concerns with the 2 mg dosage strength for EVZIO naloxone hydrochloride auto-injector.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, Supplement 7, which proposes the addition of a 2 mg dosage strength of EVZIO naloxone hydrochloride auto-injector, may be approved.

1.3.2 Additional Non Clinical Recommendations

1.3.3 Labeling

The currently approved drug product labeling is in a hybrid form of the PLLR format (b) (4). From a nonclinical perspective, the proposed label in the EDR contains the same language as the approved label for the 0.4 mg dose with additional descriptive language for the 2.0 mg

dose. In the initial NDA the Applicant submitted their currently approved drug product labeling. Prior to filing, the Agency required them to submit the labeling in PLLR format. The Applicant submitted PLLR formatted labeling in SDN 201 (CDER Stamp Date July 1, 2016). The labeling recommendations below are based on the emailed proposed labeling, as that is the label the Agency is currently reviewing. The following labeling recommendations are outlined below:

Applicant's proposed labeling (January 2016)	Reviewer's proposed changes	Rationale for changes
<p>(Highlights) INDICATIONS AND USAGE Evzio is and opioid antagonist indicated for . . .</p>	<p>(Highlights) INDICATIONS AND USAGE Evzio is an opioid antagonist indicated for . . .</p>	<p>No changes because the established pharmacological class was used.</p>
<p>USE IN SPECIFIC POPULATIONS</p>	<p>USE IN SPECIFIC POPULATIONS</p>	
<p>8.1 Pregnancy (b) (4) <i>Risk Summary</i></p> <p>The limited available data on naloxone use in pregnant women are not sufficient to inform drug-associated risk. However, there are (b) (4) [see <i>Clinical Considerations</i>]. In animal reproductive studies, no embryotoxic or teratogenic effects were observed in mice and rats treated with naloxone hydrochloride during the period of organogenesis at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg.</p>	<p>8.1 Pregnancy (b) (4) <i>Risk Summary</i></p> <p>The limited available data on naloxone use in pregnant women are not sufficient to inform a drug-associated risk. However, there are (b) (4) [see <i>Clinical Considerations</i>]. In animal reproductive studies, no embryotoxic or teratogenic effects were observed in mice and rats treated with naloxone hydrochloride during the period of organogenesis at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg.</p> <p>There are no adequate and well-controlled studies with EVZIO in pregnant women. Animal studies were conducted with naloxone hydrochloride given during organogenesis in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day. These studies</p>	<p>(b) (4)</p> <p>This review only provides recommendations on the nonclinical component of the risk summary statement. The clinical and maternal health team will provide recommendations regarding the clinical components of the risk summary statement and human data section.</p> <p>(b) (4)</p> <p>Current standard language for PLLR labels has been added as per the MHT recommendations.</p>

<p>The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.</p> <p><i>Clinical Considerations</i></p> <p>Naloxone hydrochloride crosses the placenta, and may precipitate withdrawal in the fetus as well as in the opioid-dependent mother. The fetus should be evaluated for signs of distress after EVZIO is used. Careful monitoring is needed until the fetus and mother are stabilized.</p> <p><i>Data</i></p> <p><u>Animal Data</u></p> <p>Naloxone hydrochloride was administered during organogenesis to mice and rats</p>	<p>demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.</p> <p>(b) (4)</p> <p>The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.</p> <p><i>Clinical Considerations</i></p> <p>Naloxone hydrochloride crosses the placenta, and may precipitate withdrawal in the fetus as well as in the opioid-dependent mother. The fetus should be evaluated for signs of distress after EVZIO is used. Careful monitoring is needed until the fetus and mother are stabilized.</p> <p><i>Data</i></p> <p><u>Animal Data</u></p> <p>Naloxone hydrochloride was administered during</p>	<p>(b) (4)</p>
---	--	----------------

<p>at (b) (4) doses 4-times and 8-times, respectively, the dose of 10 mg/day given to a 50 kg human (when based on body surface area or mg/m²). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.</p> <p>(b) (4)</p>	<p>organogenesis to mice and rats at (b) (4) doses 4-times and 8-times, respectively, the dose of 10 mg/day given to a 50 kg human (when based on body surface area or mg/m²). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.</p> <p>(b) (4)</p>	
<p>12.1 Mechanism of Action Naloxone hydrochloride is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites. (b) (4)</p> <p>(b) (4)</p>	<p>12.1 Mechanism of Action Naloxone hydrochloride is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites. (b) (4)</p> <p>(b) (4)</p>	<p>The Applicant proposes to add the statement in blue based on queries made to the company. However, this type of statement is not included in all other naloxone labels and (b) (4)</p> <p>(b) (4)</p>
<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility <u>Carcinogenesis</u> Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed.</p> <p><u>Mutagenesis</u> Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte</p>	<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility <u>Carcinogenesis</u> Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed.</p> <p><u>Mutagenesis</u> Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte</p>	<p>No changes from the referenced product, the original NARCAN label.</p>

<p>chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.</p> <p>Impairment of Fertility</p> <p>(b) (4)</p>	<p>chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.</p> <p>Impairment of Fertility</p> <p>(b) (4)</p> <p>-Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m²) demonstrated (b) (4)</p> <p>o adverse effect of naloxone hydrochloride on fertility.</p>	<p>The information they added in their revised PLLR labeling is (b) (4)</p>
--	--	---

2 Drug Information

2.1 Drug

CAS Registry Number
51481-60-8

Generic Name
Naloxone hydrochloride

Code Name

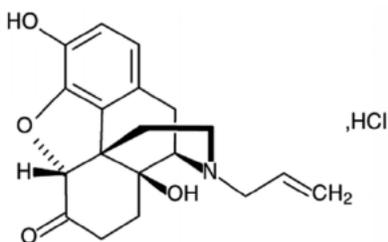
Chemical Name

(b) (4)

17-Allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride (b) (4)

Molecular Formula/Molecular Weight
C₁₉H₂₁NO₄ · HCl (b) (4) g/mol

Structure or Biochemical Description



Pharmacologic Class

Opioid antagonist (Established Pharmacologic Class)

2.2 Relevant INDs, NDAs, BLAs and DMFs

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

NDA	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
16636	NARCAN (Naloxone HCl) Injection	DAAAP	0.02, 0.4, and 1 mg/mL (IV, IM, SC)	Withdrawn FR Effective	August 20, 2010	The complete and partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids and diagnosis of suspected or known acute opioid overdosage.	Adapt Pharma (formerly Endo)

ANDA	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
72076	Naloxone HCl	OGD	1 mg/mL (Injection)	Approved	March 24, 1988	(b) (4)	International Medication System

DMF#	Subject of DMF	Holder	Submit Date (Status)	Reviewer's Comment
(b) (4)	(b) (4)	(b) (4)	October 31, 2007 (active)	LOA provided. DMF was deemed adequate in several FDA approved solutions.
(b) (4)	(b) (4)	(b) (4)	April 24, 2007 (active)	LOA provided. Deemed adequate in several FDA approved solutions.
(b) (4)	(b) (4)	(b) (4)	September 11, 1995 (active)	LOA provided. This MF covers the plunger. DMF was deemed adequate for several FDA approved solutions.
(b) (4)	(b) (4)	(b) (4)	January 25, 1972 (active)	LOA provided. Deemed adequate for several FDA approved solutions.

2.3 Drug Formulation

The following tables illustrate the composition of the 0.4 and 2.0 mg dose strength formulations of EVZIO Naloxone Hydrochloride Auto-Injector (from the Applicant's submission):

Table 3.2.P.1-1. 0.4 mg Strength NAI Drug Constituent Component Ingredients

Component	Function	Amount	Specification
Naloxone HCl, (b) (4)	Active	1 mg/mL	USP, EP
Sodium Chloride	(b) (4)	(b) (4)	USP/NF, EP
Hydrochloric Acid			USP/NF, EP
Water for Injection			USP/NF, EP
(b) (4)			(b) (4)

Table 3.2.P.1-2. 2.0 mg Strength NAI Drug Constituent Component Ingredients

Component	Function	Amount	Specification
Naloxone HCl, (b) (4)	Active	5 mg/mL	USP, EP
Sodium Chloride	(b) (4)	(b) (4)	USP/NF, EP
Hydrochloric Acid			USP/NF, EP
Water for Injection			USP/NF, EP
(b) (4)			(b) (4)

As shown in the tables above, the 2.0 mg dose contains a higher concentration of naloxone hydrochloride (5 mg/mL) compared to the original approved 0.4 dose product (1 mg/mL). Each dose is delivered in 0.4 mL. As per the current labeling, there is technically no maximum daily dose. The dosing instructions note that there is no response to the initial dose after 2 to 3 minutes, administer additional doses using a new auto-injector. If the patient is still not responsive, additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives. All the excipients are the same, which are sodium chloride, hydrochloric acid, and water for injection.

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance Specifications

As is the naloxone hydrochloride drug substance used in the approved 0.4 mg dose product, drug substance for the proposed 2.0 mg dose product is from (b) (4) (DMF (b) (4)). As such, the drug substance specifications were not changed from the

original approved of the 0.4 mg dose product. Thus, there are no additional nonclinical safety concerns with the drug substance specifications.

Drug Product Specifications

The following tables illustrate the drug product specifications from the original approved 0.4 mg dose product and the proposed 2.0 mg dose product (modified from the Applicant’s submission):

Table 3.2.P.5.1-1. Quality Control Specifications for NAI, 0.4 mg

Test	Analytical Procedure	Acceptance Criterion	NAI Release	Drug Constituent Component and NAI Stability/Shelf Life
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	(b) (4) NMT (b) (4) %	X ^a	
		NMT %		
		Single Unspecified: NMT %		
Total Impurities: NMT %				
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	(b) (4) NMT (b) (4) %		X
		NMT %		
		Single Unspecified: NMT %		
Total Impurities: NMT %				

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

Table 3.2.P.5.1-2. Quality Control Specifications for NAI, 2.0 mg

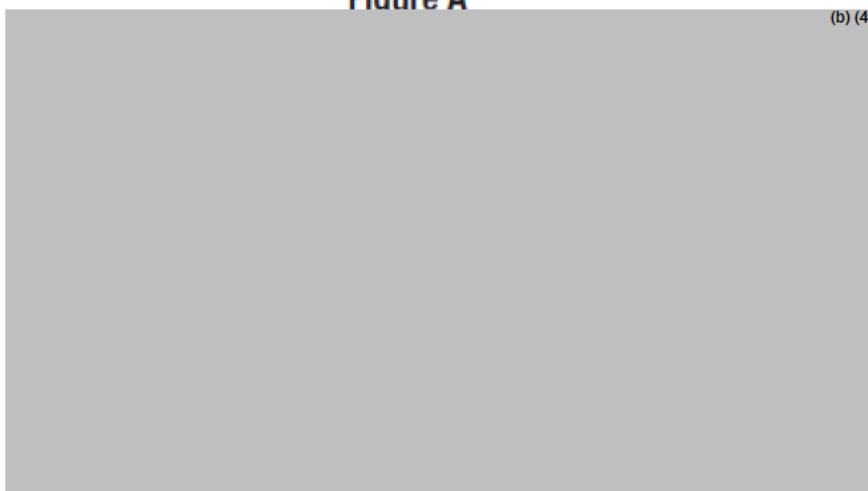
Test	Analytical Procedure	Acceptance Criterion	NAI Release	Drug Constituent Component and NAI Stability/Shelf Life
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	(b) (4) NMT (b) (4) % NMT % NMT % NMT % NMT % Single Unspecified: NMT % Total Impurities: NMT %	X ^a	
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	(b) (4) NMT % NMT % NMT % NMT % NMT % Single Unspecified: NMT % Total Impurities: NMT %		X

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

As shown in the tables above, the drug product specifications at release are identical between the approved 0.4 mg dose and the proposed 2.0 mg dose. Moreover, the drug product specifications at release meet ICH Q3B(R2) qualification thresholds of NMT 1.0% or 50 mcg (whichever is lower) for drug products with a maximum daily dose of < 10 mg/day as well as of NMT 0.5% or 200 mcg (whichever is lower) for drug products with a maximum daily dose of 10 to 100 mg/day. Thus, there are no nonclinical safety concerns with the drug product specifications.

Container Closure System

The container closure is identical for both the approved 0.4 mg dose product and the proposed 2.0 mg dose product and is illustrated in the following figure (from the Applicant’s submission in the EDR):

Figure A

The assessment of extractables/leachables was performed in the same manner for both the approved 0.4 mg dose product and the proposed 2.0 mg dose product. The reader is referred to the previous review for the extractables and leachables identified and the toxicological risk assessment of the leachables (see nonclinical review dated March 20, 2014). Briefly, the leachables of the 0.4 mg dose product (INLG02) that were identified under long-term storage conditions were $(b) (4)$ ($< (b) (4)$ mcg/mL) at the initial and 6-month timepoint and $(b) (4)$ ($< (b) (4)$ mcg/mL) at the 12 month timepoint.

The Applicant tested 1 batch (D01161A) of the proposed product (2.0 mg dose) at release and on stability for up to 36 months under normal storage conditions ($25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$). To date, data for 12 months have been submitted. The only leachable detected above 1 ppm was $(b) (4)$ ($< (b) (4)$ ppm = $< (b) (4)$ mcg/mL) at release. In the stability lot, $(b) (4)$ was detected ($< (b) (4)$ mcg/mL) at 6 months and both $(b) (4)$ were detected (both at $< (b) (4)$ mcg/mL) at 12 months. At the maximum daily dose of 2 EVZIO auto-injectors/day, the maximum daily amount of $(b) (4)$ is $< (b) (4)$ and $< (b) (4)$ mcg/mL, respectively. As the level of $(b) (4)$ is within the levels the Agency has deemed acceptable $(b) (4)$ (NMT $(b) (4)$ mcg/L as per $(b) (4)$), there are no nonclinical safety concerns with the container closure.

2.6 Proposed Clinical Population and Dosing Regimen

The new formulation of EVZIO is administered initially using the auto-injector to adult or pediatric patients intramuscularly or subcutaneously in the thigh to deliver a dose of 2.0 mg. If the desired response is not obtained after 2 or 3 minutes, additional doses may be administered using a new auto-injector, each, at 2 or 3 minute intervals until emergency personnel arrives. The label did not describe a maximum daily dose for naloxone. The proposed product is for a life-saving indication.

EVZIO is for adults and pediatric patients.

2.7 Regulatory Background

EVZIO Naloxone Auto-Injector (NAI), 0.4 mg and was approved on April 3, 2014 for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, and for immediate administration as emergency therapy in settings where opioids may be present via the IM or SC route. Naloxone hydrochloride was originally approved as NARCAN injection (NDA 16636) in April 13, 1971 for the treatment of known or suspected narcotic overdose via the IV, IM, or SC route of administration. The NARCAN NDA was withdrawn from the market but not for reasons of safety or efficacy. There is an extensive clinical experience with naloxone hydrochloride via the IV, IM, and SC routes. The reader is referred to the original nonclinical review that was written by Dr. Carlic K. Huynh and dated March 20, 2014 for details to the regulatory background of this drug product.

11 Integrated Summary and Safety Evaluation

There were no nonclinical studies submitted in this NDA. The formulation is identical to the approved 0.4 mg dosage strength formulation with the exception of 2 mg of naloxone hydrochloride in this submission. The drug substance and drug product specifications are identical to the approved 0.4 mg dosage strength product. The container closure is identical to the approved 0.4 mg dosage strength product, the extractable assessment was done appropriately with harsh solvents, and the leachable profile is not worse than the currently approved drug product. (b) (4) has been detected in the leachable studies but the levels do not represent a nonclinical safety concern. Moreover, the proposed product is for a life-saving indication. Therefore, there are no additional nonclinical concerns with the 2 mg dosage strength for EVZIO naloxone hydrochloride auto-injector. From a pharmacology toxicology perspective, the 2 mg dosage strength of EVZIO naloxone hydrochloride auto-injector is recommended for approval.

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

/s/

CARLIC K HUYNH
09/26/2016

ELIZABETH BOLAN
09/26/2016

RICHARD D MELLON
09/26/2016
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205787 Applicant: Kaleo Inc.

Stamp Date: April 19, 2016

Drug Name: EVZIO NDA/BLA Type: 505(b)(2)
(Naloxone HCl) Auto-Injector,
2.0 mg

DAAAP/ODEII/OND/CDER/
OMPT/FDA

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		No nonclinical studies were required. This supplement seeks to add a higher dosage strength to the Applicant's already approved EVZIO product.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. The Applicant did not conduct any new nonclinical studies.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Not applicable. The Applicant did not conduct any new nonclinical studies.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable. The Applicant did not conduct any new nonclinical studies.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

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

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

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		The Applicant's proposed labeling is the same as the referenced product NARCAN (add NDA 16636) for the pharmacology/toxicology sections.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		The drug substance and drug product specs have not changed.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505 (b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			Not applicable. The original NDA is a 505(b)(2) NDA that relied on the Agency previous finding of safety for NARCAN Injection and published literature. This supplement also relies upon the same data to support the proposed higher dose.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Carlic K. Huynh, PhD 5/18/2016

 Reviewing Pharmacologist Date

Elizabeth A. Bolan 5/18/16

 Team Leader/Supervisor Date

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

/s/

CARLIC K HUYNH
05/19/2016

ELIZABETH BOLAN
05/19/2016

RICHARD D MELLON
05/19/2016