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APPLICATION NUMBER:

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NON-CLINICAL 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:	215457
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Applicant's letter and CDER Stamp date:	August 31, 2021 (SDN 1), November 1, 2021 (SDN 5), and January 7, 2021 (SDN 13)
Product:	Naloxone Auto-Injector 10 mg
Indication:	(b) (4)
Applicant:	Kaleo, Inc.
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The Applicant, Kaleo, Inc., is submitting this NDA for a naloxone hydrochloride single-use auto-injector that is a higher naloxone strength (10 mg; 25 mg/mL) compared to the Applicants lower strength naloxone auto injectors. The original proposed indications for this auto-injector is for (b) (4) Naloxone hydrochloride was first approved by the FDA in 1971 for intravenous, intramuscular, and subcutaneous administration. Although there is extensive experience with naloxone hydrochloride injection, the proposed drug product would be the first that would inject a 10 mg naloxone dose with a 25 mg/mL solution via the subcutaneous or intramuscular route of administration.

1.2 Brief Discussion of Nonclinical Findings

The Applicant submitted a local intramuscular tolerance study in rabbits, an extractables and leachables assessment, and an elemental impurities assessment in support of this marketing NDA. It is noted that the Applicant addressed the systemic safety of the higher naloxone dose via clinical literature (see Medical Officer review).

The proposed naloxone drug formulation does not contain any novel excipients. For the purposes of safety qualification of impurities, degradants, excipients, and leachables for this drug product, the maximum daily dose will be 10 mg/day. The proposed specifications for drug substance impurities meet ICH Q3A(R2) qualification thresholds. There are specifications for 3 unidentified drug product degradants above the identification threshold but below the qualification threshold that will be identified postmarketing (see quality review). The stability specification (b) (4) exceeds the ICH qualification threshold of not more than (NMT) 0.5% or 200 mcg/day, whichever is lower. The Applicant did not provide qualification data to support this proposed specification. Rather, the Applicant cites a USP monograph for a naloxone injectable product that refers to a limit of NMT 4%. It is not clear to the review team what that specification is based on and we are aware that this specification is not consistent with recent specifications for the referenced drug product. Given the critical need for this life-saving drug product and existing information that suggests the lack of significant concern for the specification, the lack of definitive data to support the proposed (b) (4)% specification is not considered an approval issue. However, postmarketing requirements are proposed to definitively support the (b) (4) specification of (b) (4)%.

The proposed container closure used in the proposed drug product is the same container closure used for the lower strength EVZIO products. An extractables and leachables assessment was conducted for the 10 mg Naloxone Auto-Injector (NAI). The analytical evaluation threshold (AET) was appropriately determined. A controlled extractable study was performed on the primary container components (glass cartridge, rubber stopper, and rubber cap). These components underwent extraction and were analyzed for volatile, semi-volatile, non-volatile, and elemental extractable compounds. Based on the extractable compounds identified, a leachable evaluation was performed on three batches at multiple timepoints. The leachable compounds identified were below the 5 mcg/day threshold at the maximum daily dose in multiple batches at several timepoints. These data obtained with the higher naloxone concentration are comparable to the leachable profile obtained for the lower strength naloxone products that also showed no leachable compounds above the 5 mcg/day qualification threshold at multiple timepoints during stability. Therefore, there are no safety concerns or issues for the container closure system.

The elemental impurities assessment indicates that all appropriate elemental impurities were evaluated and determined to be below the ICH Q3D permissible limits with the exception (b) (4) Acceptable limits (b) (4) ((b) (4) mcg/day at the maximum daily dose, respectively) were determined from dietary intakes and application of a 10x safety factor taking into consideration the change in oral and intramuscular routes of administration for these elementals ((b) (4) mg/day (b) (4) and (b) (4) mg/day (b) (4)) and bioavailability. As such, the elemental impurities assessment is acceptable.

In a local intramuscular tolerance study, 3 male New Zealand White rabbits were injected with saline control (Injection Site 1) and 10 mg naloxone (Injection Site 2) on Day 1 and observed from Day 1 post-dose to the scheduled sacrifice on Day 4. The rabbits showed a very slight increase in edema from Grade 0 to Grade 1 for the control and naloxone injection (10 mg) with no change in erythema among the groups (Grade 0). All rabbits survived to the scheduled euthanasia and there were no treatment-related changes in clinical observations and body weight. Gross changes at the injection sites (dark focus) and adjacent skin (scab) were considered related to the dosing procedure and not treatment-related and microscopic changes at the injection sites (monocellular cell infiltration and hemorrhage of the subcutaneous tissue as well as degeneration/ necrosis of the fascia), skin (serocellular crust), and skeletal muscle (degeneration/ necrosis of the myofiber) were considered expected responses to needle puncture and not treatment-related. The above study did not test the local tissue toxicity of a SC injection. It is noted that the needle length for this device is approximately 0.5 inches (13 mm). The local response after IM injection suggests minimal concern, particularly given the risk:benefit for this potentially life-saving therapy. The existing human PK data also provides some degree of characterization of the local tissue response to this drug product.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, the proposed drug product may be approved with the postmarketing requirements listed below.

1.3.2 Additional Nonclinical Recommendations

The following nonclinical studies are recommended as a PREA postmarketing requirement and to definitively qualify the drug product degradant (b) (4) at the proposed stability specification:

1. Conduct a juvenile animal toxicology study in rats to support clinical dosing in pediatric patients from birth to less than 12 years of age. This study will evaluate the effects of naloxone on the developing central nervous, endocrine, and reproductive systems.

2. Conduct a GLP in vitro genetic toxicology Ames assay testing the potential for the naloxone degradant, (b) (4) to induce point mutations.

3. Conduct a GLP in vitro genetic toxicology study characterizing the potential of the naloxone degradant, (b) (4) to induce chromosomal damage.

4. Conduct a GLP repeat-dose toxicology study of at least 14 days duration in a single species to characterize the toxicologic potential of the naloxone degradant, (b) (4).

1.3.3 Labeling

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

Applicant's proposed labeling	***Reviewer's proposed changes***	***Rationale for changes***
USE IN SPECIFIC POPULATIONS	**USE IN SPECIFIC POPULATIONS**	
8.1 Pregnancy *Risk Summary* (b) (4) In animal reproduction studies, no	**8.1 Pregnancy** *Risk Summary* (b) (4) In animal reproduction studies, no	Label in the PLLR format. The safety margins in the animal reproduction studies (4- and 8-times the dose of 50 kg human given 10 mg) is correct. This referenced body weight is consistent with the referenced product labeling. The referenced Narcan injection labeling (NDA 16-363) was last updated in 2002 and is

embryotoxic or teratogenic effects were observed in mice and rats treated with naloxone HCl during the period of organogenesis at doses equivalent to 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg *[see DATA]*. 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.	embryotoxic or teratogenic effects were observed in mice and rats treated with naloxone HCl during the period of organogenesis at doses equivalent to 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg *[see DATA]*. 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.	not in PLLR format. The proposed labeling is consistent with cross-referenced EVZIO labeling (NDAs 205787 209862), which are in PLR format and NDA 209862 was last updated in 2016.
Data Animal Data Naloxone hydrochloride was administered during organogenesis to mice and rats at doses 4 times and 8 times, respectively, the dose of 10 mg/day given to a 50 kg human (when based on body surface area or mg/m^2). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.	***Data*** Animal Data Naloxone hydrochloride was administered during organogenesis to mice and rats at doses 4 times and 8 times, respectively, the dose of 10 mg/day given to a 50 kg human (when based on body surface area or mg/m^2). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.	Proposed text is identical to the cross-referenced EVZIO labeling (NDA 209862) and is acceptable.
12.1 Mechanism of Action Naloxone HCl is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites. Naloxone HCl 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.	**12.1 Mechanism of Action** Naloxone HCl is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites. Naloxone HCl 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.	Proposed text is identical to the cross-referenced EVZIO labeling (NDA 209862) and is acceptable.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed. Mutagenesis Naloxone was weakly positive in the Ames mutagenicity and in the *in vitro* human lymphocyte chromosome aberration test but was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in the *in vivo* rat bone marrow chromosome aberration study. Impairment of Fertility Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no adverse effect of naloxone HCl on fertility.	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed. Mutagenesis Naloxone was weakly positive in the Ames mutagenicity and in the *in vitro* human lymphocyte chromosome aberration test but was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in the *in vivo* rat bone marrow chromosome aberration study. Impairment of Fertility Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no adverse effect of naloxone HCl on fertility.	Proposed text is identical to the cross-referenced EVZIO labeling (NDA 209862) and is acceptable.

2 Drug Information

2.1 Drug

CAS Registry Number
51481-60-8

Generic Name
Naloxone hydrochloride (b) (4)

Code Name
N/A

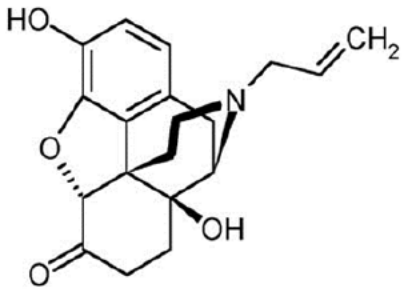
Chemical Name
17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride (b) (4)

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

(1S,5R,13R,17S)- 10,17-dihydroxy-4-(prop-2-en-1-yl)-12-oxa-4-azapentacyclo [9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$] octadeca-7(18),8,10-trien-14-one

Molecular Formula/Molecular Weight
(b) (4)

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	Evzio (Naloxone Hydrochloride)	Active	DAAP	(b) (4)	12/16/2012	Kaleo Inc.
141770	Naloxone	Presubmission	DAAP	(b) (4)	October 19, 2018	Department of the Army

NDA	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
16636	Narcan (Naloxone Hydrochloride)	DAAP	0.2, 0.4, and 1 mg/mL (Injection)	Withdrawn	August 20, 2010	Opioid Dependence	Adapt Pharma Operations LTD
205787	Evzio (Naloxone Hydrochloride)	DAAP	0.4 mg/0.4 mL (Injection)	Approved	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	Kaleo Inc.
209862	Evzio (Naloxone Hydrochloride)	DAAP	2 mg/0.4 mL (Injection)	Approved	October 19, 2016	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	Kaleo Inc

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

2.3 Drug Formulation

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

Table 3.2.P.1.2-1:NAI 0.4 mg, 2 mg, and 10 mg Drug Constituent Component Ingredients

Component	Description	Function	Specification
Naloxone HCl, anhydrous	NAI 0.4 mg: 1 mg/mL[1] NAI 2 mg: 5 mg/mL[2] NAI 10 mg: 25 mg/mL[3]	Active	USP, EP
Sodium Chloride (NaCl)	8.35 mg/mL	(b) (4)	USP/NF, EP
HCl	*qs* ad to pH 3.0 - 4.5		USP/NF, EP
Water for Injection	*qs* ad to 1 mL		USP/NF, EP
1 2 3	(b) (4)		

The proposed product is Naloxone Auto-Injector (NAI) 10 mg. The formulation is made up of sodium chloride, water, and hydrochloric acid for pH adjustment. These excipients are adequately qualified in FDA-approved injectable products. The concentration of the naloxone drug product is 25 mg/mL for the proposed product with an injection volume of 0.4 mL that delivers 10 mg of naloxone. A maximum daily dose (MDD) of 10 mg/day has been established for this product for qualification purposes.

It is noted that the fill volume of approximately (b) (4) mL is identical across three dosage strengths and the physicochemical properties of the higher strength naloxone product is very similar to the lower strength naloxone products as seen in the table below (from the Applicant's submission):

Formulation Parameter	NAI 0.4 mg	NAI 2 mg	NAI 10 mg
Naloxone HCl concentration (mg/mL)	1	5	25
Naloxone HCl readily soluble (Y/N)	Yes		
Targeted pH adjustment	(b) (4)		
Osmolality (mOsM/kg)	(b) (4)		
Density (g/mL)			
Viscosity (mPa*s)			

(b) (4)

Due to the higher concentration of naloxone (25 mg/mL), the Applicant submitted a local tolerance study in rabbits (reviewed below).

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation

Related Substances	(n/a)	(n/a)
EP Impurity A	EP<2.2.29> VR #470	0.2% max
EP Impurity B		0.2% max
EP Impurity C		0.2% max
[illegible]	[illegible]	[illegible]

(b) (4)

(b) (4)

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

Degradant	Stability Specification	Adequacy
(b) (4)	NMT (b) (4) %	Adequate per ICH Q3B(R2) qualification thresholds
	NMT (b) (4) %	
	NMT (b) (4) %	
	NMT (b) (4) %	The shelf-life specifications exceed ICH Q3B(R2) qualification thresholds. See below for evaluation and discussion.
	NMT (b) (4) %	Adequate per ICH Q3B(R2) qualification thresholds;
Specified unidentified impurity with a RRT (b) (4)	NMT (b) (4) %	Although above identification threshold, these unidentified impurities (b) (4) these specifications result in levels that are below (b) (4) mcg/day acceptable intake levels for a genotoxic impurity and therefore, there are no concerns from a genotoxicity perspective.
Specified unidentified impurity with a RRT (b) (4)	NMT (b) (4) %	
Specified unidentified impurity with a RRT (b) (4)	NMT (b) (4) %	
Single Unspecified	NMT (b) (4) %	Adequate per ICH Q3B(R2) qualification thresholds
Total Impurities	NMT (b) (4) %	Defer to CMC

As shown in the table above, the drug product degradants specifications are within the ICH Q3B(R2) qualification thresholds for drug products with a maximum daily dose of 10 to 100 mg/day with the exception of the (b) (4) specification of NMT (b) (4) %. The Applicant did not provide qualification studies as recommended by the Division during development which would include a repeat-dose toxicology study of 14 days duration and a minimal genetic toxicology screen. The justification provided by the Applicant for the proposed specification was that a USP monograph for naloxone injection includes reference to a limit of not more than (NMT) 4%. The review team is

not aware of what served as the basis of this USP limit. Review of the historical records suggests that this limit is above that of the referenced drug product.

Although this specification was considered acceptable for the cross-referenced 2 mg strength drug product, that drug product was evaluated taking into consideration a maximum daily dose of 4 mg (two injections) and therefore NMT (b) (4)% would be within the ICH qualification thresholds and therefore acceptable. Of note, at that specification, a person would be exposed to (b) (4) mcg (b) (4) at a concentration of (b) (4) mcg/ (b) (4) mcL ((b) (4) mcg/mcL). For this proposed drug product, the MDD is 10 mg. At the specification of NMT (b) (4)%, a person would be exposed to (b) (4) mcg at a concentration of (b) (4) mcg/ (b) (4) mcL ((b) (4) mcg/mL). These differences are not likely to result in significantly different safety profiles. As such, although above the ICH Q3B qualification threshold, the proposed specification should not preclude an approval recommendation for this potentially life-saving drug product at this time. However, as there are no data on this impurity, an adequate qualification of the material should be completed. This can be done as postmarketing requirements if the benefit:risk is deemed acceptable.

Several unidentified impurities at RRT (b) (4) and RRT (b) (4) have a specification of NMT (b) (4)%, which is below the ICH Q3B qualification threshold. The specification of NMT (b) (4)% would confer an exposure of (b) (4) mcg/day at the maximum daily dose of 10 mg/day (10 mg/day x (b) (4) = (b) (4) mg/day = (b) (4) mcg/day), which meets ICH Q3B(R2) qualification thresholds and the maximum daily exposure of (b) (4) mcg/day is below the 120 mcg/day limit for genotoxic impurities in acute products per ICH M7. Moreover, these specified unidentified impurities (b) (4) (b) (4) Identification of compounds that exceed the identification threshold is considered a CMC issue. See CMC review for further details. Because these are below the qualification threshold and do not raise any mutagenicity concerns, the specification for the unidentified degradants is not considered an approval issue from the nonclinical pharmacology toxicology discipline. Thus, the drug product specifications are acceptable.

Container Closure System:
The proposed primary container closure is identical to the container closure used in the previous EVZIO products manufactured by the Applicant. The primary container closure system for the proposed 10 mg NAI is described in the following table (from the Applicant's submission):

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

Component	Description	DMF [a]	Supplier
Cartridge	0.5 ml, (b) (4) glass, (b) (4) (b) (4) compliant with EP and USP	(b) (4)	(b) (4)
Crimp Cap	Aluminum crimping cap (no product contact), silver in color, (b) (4) compliant with EP and USP		
Plunger	(b) (4) (b) (4) compliant with EP and USP (b) (4) (b) (4)		

[a] Letters of authorization to reference the respective DMFs are provided in Section 1.4.1.
[b] (b) (4) elastomer

As shown in the table above, the container closure system is comprised of a glass cartridge (DMF (b) (4)), crimp cap with rubber septum (DMF (b) (4)), and plunger (DMF (b) (4)). These are the only components that come in contact with the drug product solution during storage.

Extractables:
A controlled extraction study was performed on the primary container components (glass cartridge, rubber stopper, and rubber cap) as well as the manufacturing component (b) (4) Each component was (b) (4) analyzed for the volatile extractables. Moreover, each component was (b) (4) analyzed for semi-volatile and non-volatile extractables. In addition, each component was (b) (4) (b) (4) analyzed for elemental extractables. The manufacturing component was (b) (4) analyzed for volatile, semi-volatile, and non-volatile extractables. HS/GC/MS (volatiles), DI/GC/MS (semi-volatiles), UHPLC/UV/MS (non-volatiles), and ICP/MS (elemental impurities) analytical methods were used to detect extractables from the glass cartridge, rubber components, and (b) (4) during manufacturing.

The analytical evaluation threshold (AET) of (b) (4) mcg/component was used for evaluations of organic extractables from the primary container components and (b) (4) mcg/mL was used for evaluations of organic extractables from the manufacturing component. The reviewer AET of 12.5 mcg/mL is based on the 5-mcg threshold in a dose volume of 0.4 mL for the proposed product (5 mcg/0.4 mL = 12.5 mcg/mL). As such, the AETs used by the Applicant is acceptable.

Volatile Extractables by the HS/GC/MS Analytical Method:

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(b) (4)

The extractable study methods were deemed adequate by the CMC review team.

Leachables:
For all analytical methods used to detect the extractables, a leachables screening was performed. The extractable profiles from the controlled extraction study for the

components were used to inform monitoring of leachable compounds. Leachables were evaluated from three batches at 0-, 6-, and 12-month time points under long-term normal conditions (25ºC/60% RH). There were no leachables detected above the SCT in the leachable screening using the HS/GC/MS and UHPLC/UV/MS analytical methods. The following table illustrates the highest leachable levels in the proposed drug product using the DI/GC/MS analytical method (data from the Applicant's submission):

Compound	CAS number	Amount (mcg/mL)	Amount at Maximum Daily Dose (mcg/day)[1]	Adequacy
(b) (4)				Acceptable, as all leachables are below the 5 mcg/day threshold. These data also demonstrate that the leachable profile of the higher concentration formulation is not altered by the higher naloxone concentration when compared to the approved lower concentration naloxone products.

1 = The maximum daily dose is 10 mg/day or 1 application (0.4 mL)

As shown in the table above, the levels of leachables are below the recommended 5 mcg/day safety concern threshold for the proposed drug product and as such, are acceptable. These data obtained with the higher naloxone concentration are comparable to the leachable profile obtained for the lower strength naloxone products that also showed no leachable compounds above the 5 mcg/day qualification threshold at multiple timepoints during stability. The CMC review team concluded that leachable study methodology and resulting data were adequate and appropriate to inform the nonclinical risk assessment.

Elemental Impurities Assessment:
Elemental impurities were evaluated from a NAI 10 mg batch at the 12-month stability timepoint. The following table illustrates the elementals that were analyzed (from the Applicant's submission):

Class	Element Abbreviation	Element	Parenteral PDE (µg/day)
(b) (4)			

The following table summarizes the elemental impurities detected in the proposed drug product above (b) (4) ng/mL (data from the Applicant's submission):

Element	Amount Detected (mcg/mL)	Amount at the Maximum Daily Dose (mcg/day)[1]	ICH Q3D Parenteral PDE (mcg/day)
(b) (4)			No PDEs established due to their low inherent toxicity; acceptable
			Acceptable, see risk assessment below
			Acceptable, see risk assessment below
			(b) (4) mcg/day; acceptable
			(b) (4) mcg/day; acceptable
			(b) (4) mcg/day; acceptable

1 = The maximum daily dose is 10 mg/day or 1 application (0.4 mL)

As shown in the table above, the levels of the elements (b) (4) meet ICH Q3D limits and as such, are acceptable. The elements (b) (4) were not detected via appropriately sensitive assays (see CMC review).

For (b) (4) no PDEs were established due to their low inherent toxicity per ICH Q3D. As such, these levels are acceptable.

For (b) (4) the mean dietary intake (b) (4) ranges from (b) (4) mg/day[1]. However, the proposed drug product is not an oral product and applying a safety factor of 10x for difference in route of administration and taking into consideration bioavailability, an acceptable daily intake (b) (4) based on dietary daily intake is calculated to be (b) (4) to (b) (4) mg/day. As such, the amount (b) (4) from the maximum daily dose of the proposed product ((b) (4) mcg/day) does not pose a safety concern and is deemed acceptable.

For (b) (4) the dietary intake (b) (4) is (b) (4) mg/day and the normal average intake range (b) (4) from drug products is (b) (4) mg/day[2] and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has determined a provisional tolerable weekly intake of (b) (4) mg/kg from which (b) (4) mg/kg/day is assumed for a daily intake (b) (4) which confers (b) (4) mg/day for an average human weighing 60 kg. However, the proposed drug product is not an oral product and applying a safety factor of 10x for difference in route of administration and taking into consideration bioavailability, an acceptable daily intake (b) (4) based on dietary daily intake is calculated to be (b) (4) mg/day. As such, the amount (b) (4) from the maximum daily dose of the proposed drug product ((b) (4) mcg/day) does not pose a safety concern and is deemed acceptable.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population of the proposed drug product is adult and pediatric patients 12 years of age and over. The following is the originally proposed indications from the Applicant:

(b) (4)

1 (b) (4)

2 (b) (4)

3 (b) (4)

(b) (4)

2.7 Regulatory Background

Naloxone HCl was originally approved in since 1971 and first marketed by Endo (now Adapt Pharma Operations LTD) as Narcan® injection (NDA 016636). Naloxone HCl injection has become available as a generic drug with various concentrations manufactured by a number of companies. The Applicant developed the original naloxone autoinjector (NAI) 0.4 mg, which was approved on April 3, 2014 (NDA 205787). A subsequent NAI 2.0 mg strength was approved on October 19, 2016 (NDA 205787, Supplement 7; cross referenced to NDA 209862). The proposed product is a NAI that delivers a 10 mg (NDA 215457) dose. This is a 505(b)(2) application relying upon the Agency's previous finding of safety and efficacy for Narcan injection (NDA 16636).

Drug development recommendations for this proposed drug product were provided in the context of two INDs: IND 112292 (Kaleo), and preIND 141770 (Department of the Army). Minutes from relevant meetings conducted under both INDs were submitted with this NDA application and key nonclinical recommendations are summarized below:

A preIND meeting (PIND 141770) was held on December 13, 2018 with the Department of the Army. Because specific device and drug product details were not available at that time, the following general nonclinical comments were communicated with the Applicant (adapted from the meeting minutes dated January 11, 2019):

1. Impurities and degradants should be qualified as recommended in the relevant ICH guidelines.

2. Because the drug product will result in a higher concentration of naloxone than any referenced drug product, local tissue toxicity assessment should be completed.

3. Because the drug product may result in higher systemic exposures to naloxone than any referenced drug product, the systemic safety should be justified. This could be addressed via nonclinical studies or, if available and adequate, previous human experience and/or literature.

4. Adequate data to justify the safety of the container closure system should be provided. This usually includes extractable and leachable assessments (with toxicological risk assessment for any leachable detected above the 5 mcg/day threshold).

A preNDA meeting conducted under IND 112292 was held on February 24, 2020 with the Applicant Kaleo and representatives supporting the Department of the Army. As per the meeting minutes dated March 25, 2020, the Agency reiterated the above PIND recommendations and noted that it may be possible to justify the safety the container closure system by bridging data that demonstrates comparable profiles compared to the previously approved EVZIO drug products. It was also noted that submission of a detailed elemental risk impurity risk assessment report will be reviewed with the NDA submission.

There is an agreed upon PSP for the proposed product (IND 112292; see Pediatric Study Plan – Initial Agreement document dated September 20, 2021). We note that the Applicant has committed to conducing a juvenile animal study to support dosing for a pediatric age range between 0 to 12 years of age as a postmarketing requirement.

3 Studies Submitted

3.1 Studies Reviewed

Local tolerance study in rabbits and an extractables and leachables assessment.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

There were no previous reviews referenced.

4 Pharmacology

4.1 Primary Pharmacology

There were no new primary pharmacology studies conducted with naloxone submitted in this NDA with the exception of a research study conducted in collaboration with the Applicant, which is reviewed below.

Carfentanil toxicity in the African green monkey: Therapeutic efficacy of naloxone (Langston et al., 2020)

Adult male African green monkeys were used in a series of experiments. The first experiment determined the median effective dose, ED_{50} (0.71 mcg/kg), of subcutaneous injection of carfentanil to the back or flank for inducing bradypnea and/or loss of posture. Bradypnea (abnormally slow breathing rate) as an endpoint appears to be appropriate as respiratory depression is a dangerous effect of opioid overdose. However, bradypnea/loss of posture may or may not be considered a lethal endpoint of

carfentanil. A total of 11 monkeys were dosed with carfentanil in the first experiment. Of these, 5 monkeys required treatment with naloxone and 1 monkey died within 70 min of administration of 0.794 mcg/kg of carfentanil due to cardiorespiratory failure despite attempts at revival with naloxone therapy and cardiopulmonary resuscitation.

The second experiment attempted to establish the ED_{50} of naloxone for rapidly reversing the bradypnea/loss of posture induced by carfentanil (1.15 mcg/kg). The third experiment evaluated the effects of carfentanil (0.575 mcg/kg) alone, the safety of naloxone (71 to 2841 mcg/kg), and the efficacy of naloxone (71 to 710 mcg/kg) administration at two time points following carfentanil (1.15 mcg/kg) on operant choice reaction time. It is noted these studies are not GLP-compliant and no NOAEL was determined. The concentrations of naloxone tested ranged from 1 to 40 mg/mL. The proposed product concentration is 25 mg/mL.

The following table shows different clinical signs of reversal of carfentanil intoxication by the different doses of naloxone used (from the publication):

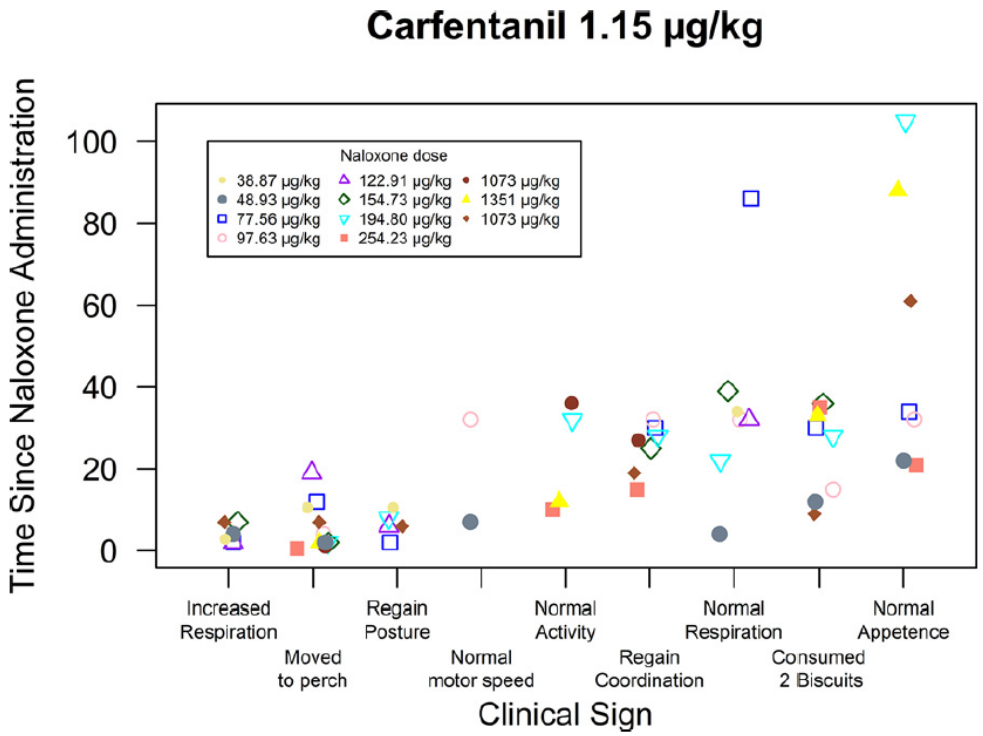

Fig. 3. Latencies (in minutes) to the reversal of carfentanil intoxication. Naloxone doses ranged from 39 µg/kg to 1351 µg/kg. Individual monkeys are represented by a unique symbol-color combination consistent with those in Fig. 2.

The above figure demonstrates no clear dose-dependency with the time since naloxone administration to reversal of each clinical sign.

In the third experiment, the researchers attempted to characterize the time course of carfentanil intoxication and the efficacy of naloxone in attenuating carfentanil intoxication and restoring behavioral function. Six extensively trained male monkeys were used for behavioral assessments. Each of these monkeys were dosed with either carfentanil 0.575 or 1.15 mcg/kg (1.6x ED_{50} for bradypnea/loss of posture) followed by naloxone at either 8 min post carfentanil dose (immediate treatment) or at the onset of bradypnea/loss of posture (delayed treatment). Immediate Treatment represents early treatment. Delayed Treatment represents buddy aid or emergency response treatment at the onset of severe or obvious opioid effects.

Carfentanil alone, even at the lower dose of 0.575 mcg/kg, produced prompt and nearly complete suppression of the operant response measures. Carfentanil challenge dose (1.15 mcg/kg) followed by naloxone at doses of 71 and 142 mcg/kg (1.6 and 3.2 mg HED) only partially or briefly reversed the carfentanil-induced behavioral suppression for both immediate and delayed treatment times. Carfentanil challenge dose (1.15 mcg/kg) followed by naloxone at or above 355 mcg/kg (8 mg HED) provided complete reversal of carfentanil effects on choice reaction-time performance and was sustained throughout the 2 h behavioral assessment period following both immediate and delayed treatment times. Based on the time course data, the functionally effective naloxone dose for the treatment of carfentanil intoxication across both treatment conditions (immediate and delayed) was 355 mcg/kg (8 mg HED). The results with the carfentanil challenge are illustrated in the following figures (Figures 5 and 6 from the publication):

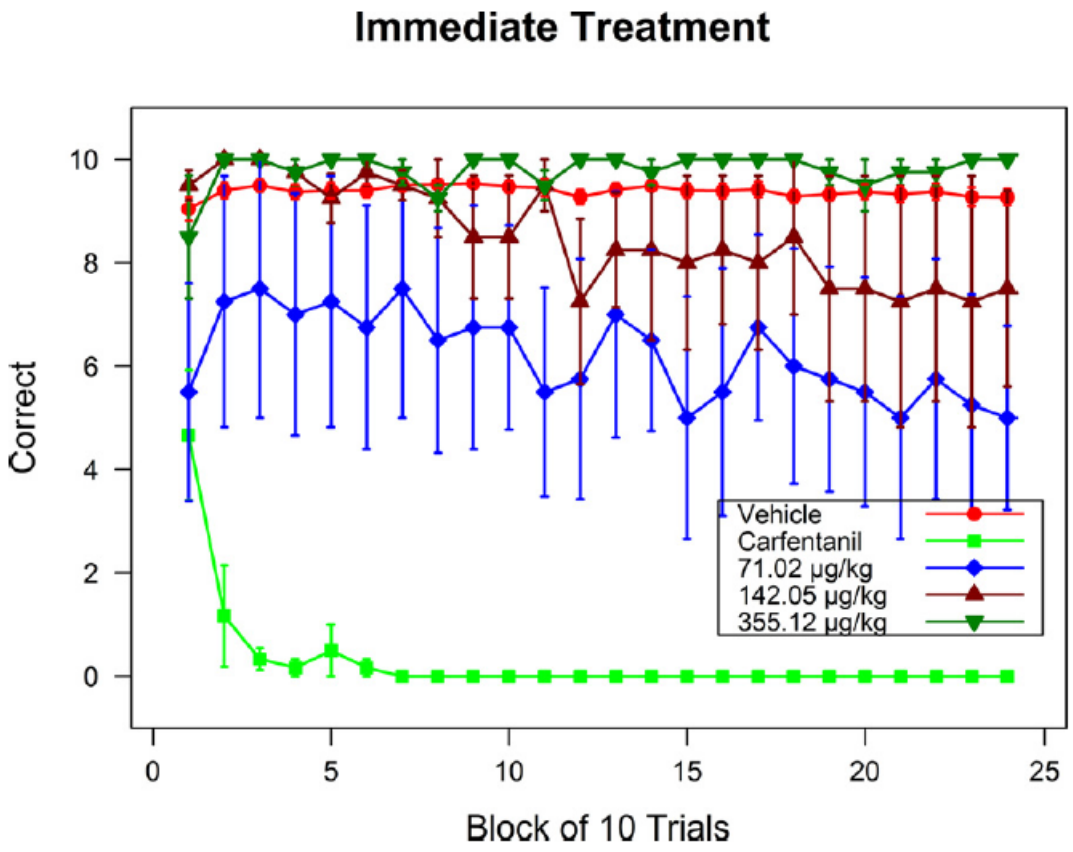

Fig. 5. Correct reaction-time responses collapsed across blocks of 10 trials and animals (n = 4-6/point) when naloxone (71, 142, or 355 µg/kg) was administered at a fixed time (8 min) following carfentanil administration. Error bars are ± SEM and where not visible, error bars are subsumed by the symbol.

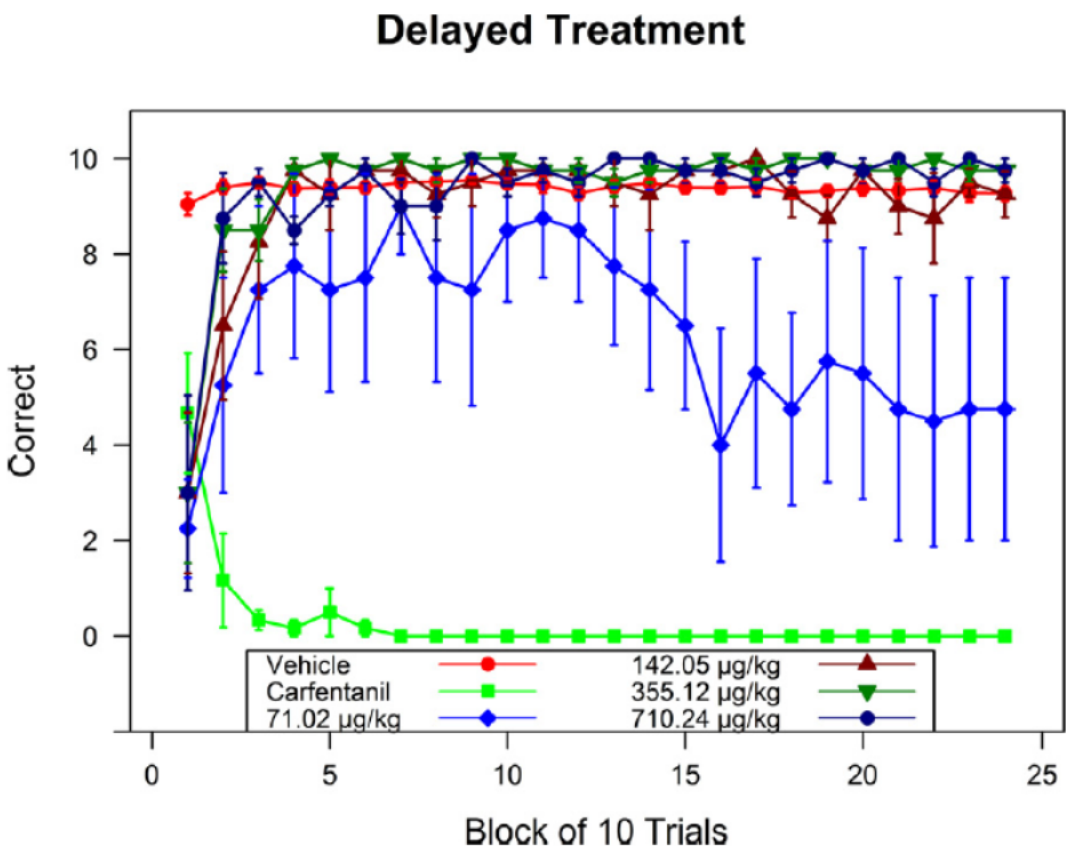

Fig. 6. Group mean correct responses (± SEM) across blocks of 10 trials as a function of experimental condition (n = 4-6/point). Doses of naloxone spanned a 10-fold range (71-710 µg/kg) and were administered at the onset of bradypnea or loss of posture. For other details see caption of Fig. 5.

The researchers used a wide range of doses for naloxone, with the dose range of naloxone used (71 to 2841 mcg/kg; 1 to 40 mg/mL concentration) in the monkeys, via SC administration, which is equivalent to 2 to 80 mg in humans based on a body surface area comparison using a 60 kg human using the equation described in the FDA start dose guidance.

Naloxone Doses (mcg/kg)	HED (mg)
71.02	2
142.04	4
355.12	10
710.24	20

1420.48	40
2840.96	80

The range of naloxone (dose range and concentration range) used by the researchers appears adequate. The toxicological endpoints of this experiment appear to be monitoring of the monkey's activity and posture. Although not a typical toxicology study, the researchers used a clinically relevant endpoint of bradypnea (abnormally slow breathing rate) to mimic the respiratory depression often seen with opioid use; however, bradypnea alone does not likely adequately represent carfentanil exposures equivalent to an overdose scenario.

Although the behavioral endpoint showed some promise in demonstrating dose dependency of naloxone treatment of carfentanil-induced toxicity in the third experiment, there are several issues. The study may not have tested a high enough carfentanil dose. The behavioral endpoints (yawn, face on cage, starring, slow blink, hunch, decreased respiration (by approximately 25%), slow movement, prone, muscle rigidity, and bradypnea) although clinically relevant do not represent the extent of carfentanil pharmacodynamics that could occur in a fatal overdose scenario. The death reported in the first experiment was in a monkey that received carfentanil (0.794 mcg/kg) that was below the carfentanil challenge dose (1.15 mcg/kg). The data do not show that the proposed dose of 10 mg naloxone will reverse carfentanil overdose (the dose of carfentanil tested in this publication is not a dose representative of an overdose). No blood levels of either compound (carfentanil or naloxone) were measured in this publication.

The Applicant submitted a review citing multiple published studies describing the pharmacology of naloxone. These were evaluated as part of this review and determined to not impact current nonclinical portions of the drug product labeling. The reader is referred to the reviews by the clinical team and the Division of Applied Regulatory Science (DARS) for discussion of the efficacy of this drug product.

4.2 Secondary Pharmacology

There were no new secondary pharmacology studies with naloxone submitted in this NDA. The Applicant submitted a review citing multiple published studies. These were evaluated as part of this review and determined to not impact current nonclinical portions of the drug product labeling.

4.3 Safety Pharmacology

There were no new safety pharmacology studies with naloxone submitted in this NDA. The Applicant submitted a review citing multiple published studies. These were evaluated as part of this review and determined to not impact current nonclinical portions of the drug product labeling.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

There were no new PK/ADME studies with naloxone submitted in this NDA. The Applicant submitted a review citing multiple published studies. These were evaluated as part of this review and determined to not impact current nonclinical portions of the drug product labeling.

5.2 Toxicokinetics

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

6 General Toxicology

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

Applicant submitted a literature review citing a single published intranasal toxicology study (Bariev et al., 2020). The published study tested a total of 10 doses of 0.1 mg naloxone hydrochloride via intranasal instillation to Wistar rats at 45-minute intervals. Animals were observed for two weeks after this initial series of treatments. As per the authors, the cumulative dose administered to male rats was 36.6 mg/kg and female rats was 39.4 mg/kg. These doses correspond to a human equivalent dose of 354 mg in males and 381 mg in females based on a body surface area comparison and assuming a 60 kg person. The published study included data on clinical signs, body weights, some biochemical parameters, and gross macroscopic examination of internal organs. No significant abnormalities were noted; however, given the limitations of the study design, this study is not adequate to support the proposed drug product.

Therefore, the safety of the proposed dose will have to be based on any relevant human data (see Medical Officer review for review of human data for the systemic safety of the 10 mg naloxone dose).

7 Genetic Toxicology

There were no new genetic toxicology studies with naloxone submitted in this NDA. No new data were identified in the published literature review.

8 Carcinogenicity

There were no new carcinogenicity studies with naloxone submitted in this NDA. No new data were identified in the published literature review.

9 Reproductive and Developmental Toxicology

There were no new reproductive and developmental toxicology studies with naloxone submitted in this NDA. The Applicant submitted a review citing multiple published studies. These were evaluated as part of this review and in previous reviews of the cross-referenced drug product applications and determined to not impact current nonclinical portions of the drug product labeling.

10 Special Toxicology Studies

Local Tissue Safety

The Applicant's submission states that the formulation of the proposed 10 mg drug product is almost identical to the previously approved cross-referenced EVZIO drug products with the exception of the concentration of naloxone, the resulting slightly higher osmolality, and viscosity. They state that the osmolality is within generally accepted tolerability ranges for hypertonic injectables (Wang et al., 2015).

The Applicant also submitted human pharmacokinetic studies testing the drug product formulation. These data also inform the local tissue safety of the proposed higher concentration.

In addition, a local intramuscular tolerance study in rabbits (Study 20259407) was conducted to support the local safety of the higher naloxone concentration of 25 mg/mL.

Title: A Single Dose Local Tolerance Study of Naloxone Hydrochloride by Intramuscular Injection in Rabbits (Study 20259407)

The study was GLP compliant and contained Quality Assurance statements that were signed on December 8, 2020. The study was initiated on July 14, 2020. Naloxone Hydrochloride 10 mg drug cartridge with a concentration of 25 mg/mL (Lot No. INTC01) is 99.9% pure. Male New Zealand White rabbits were approximately 27 weeks old and weighed between 2.9 to 3.4 kg at the initiation of dosing. The following table illustrates the experimental design of this local tolerance study (from the Applicant's submission):

Text Table 1
Experimental Design

Group Number	Test Material	Injection Site	Dose Level[a] (mg)	Dose Volume (mL)	Dose Concentration (mg/mL)	Number of Animals Main Study Males
1	Control[b]	1	0	0.4	0	3
	Naloxone Hydrochloride	2	10	0.4	25	

[a] Dosed once on Day 1.
[b] 8.35 mg/mL Sodium Chloride in Sterile Water for Injection, pH (b) (4)

Rabbits were given naloxone hydrochloride (Injection Site 2) or saline control (injection site 1) via intramuscular injection once on Day 1 of the study. Injections were

administered into the left quadriceps muscle (control) or right quadriceps muscle (naloxone). Prior to dosing, the area above the left and right quadricep muscles was clipped free of hair before the first dose and as often thereafter to allow for clear visualization of the injection sites. The injection sites were marked with a marker and re-marked as necessary throughout the study.

Observations and Results

Mortality

All main study rabbits were observed for mortality at least twice daily (morning and afternoon) during the study. There were no unscheduled deaths during the study as all rabbits survived to the scheduled euthanasia on Day 4.

Clinical Observations

Cage side observations were given to all main study rabbits once daily from Week -1 and throughout the dosing and observation periods. Cage side observations were not required on the days of detailed clinical observations during the pretreatment (prior to Day 1) and observation periods or on the day of scheduled euthanasia.

Detailed clinical observations were given to all main study rabbits at least during animal assignment, prior to dosing on Day 1, and prior to scheduled euthanasia on Day 4.

The following table illustrates all of the clinical observations that were noted (from the Applicant's submission):

Observation Type: All Types From Day 1 (Start Date) to 4 (Start Date)	Male 0/10 mg Group 1
Skin, Scab, Hindlimb, Left	
Number of Animals Affected	1
Number of Times Recorded	2
% of Affected Animals	33
First to Last seen	1 - 4
Skin, Bruise, Treatment Site No.02	
Number of Animals Affected	1
Number of Times Recorded	1
% of Affected Animals	33
First to Last seen	2 - 2

According to the Pathology Report, skin scab was due to skin irritation associated with shaving prior to dose administration in Animal No. 1002 and skin bruising was procedure related in Animal No. 1003. There were no further treatment-related changes in clinical observations.

Body Weight

Individual body weights were measured in all main study rabbits at animal assignment, prior to dosing on Day 1, and prior to scheduled euthanasia on Day 4. There were no treatment-related changes in body weight or body weight gains.

Dermal Scoring

Dermal scoring was performed immediately post-dose and at 24, 48, and 72 hours post-dose. All main study rabbits were observed in detail according to the Draize method (Draize, 1959). A final score was recorded on the day of scheduled euthanasia (Day 4). The following table illustrates the dermal scoring (from the Applicant's submission):

Observation Type: Local Irritation Ext 1 From Day 1 (Start Date) to 4 (Start Date)	Male 0/10 mg Group 1
Edema, Treatment Site No.01, Grade 0	
Number of Animals Affected	3
Number of Times Recorded	12
% of Affected Animals	100
First to Last seen	1 - 4
Erythema, Treatment Site No.01, Grade 0	
Number of Animals Affected	3
Number of Times Recorded	12
% of Affected Animals	100
First to Last seen	1 - 4

Observation Type: Local Irritation Ext 2 From Day 1 (Start Date) to 4 (Start Date)	Male 0/10 mg Group 1
Edema, Treatment Site No.02, Grade 0	
Number of Animals Affected	3
Number of Times Recorded	11
% of Affected Animals	100
First to Last seen	1 - 4
Edema, Treatment Site No.02, Grade 1	
Number of Animals Affected	1
Number of Times Recorded	1
% of Affected Animals	33
First to Last seen	2 - 2
Erythema, Treatment Site No.02, Grade 0	
Number of Animals Affected	3
Number of Times Recorded	12
% of Affected Animals	100
First to Last seen	1 - 4

Edema (Grade 0) and erythema (Grade 0) was observed in the control (Injection Site 1) and edema (Grade 0 and Grade 1) and erythema (Grade 0) was observed with naloxone (Injection Site 2). There was a slightly more severe observation of edema between the control (Grade 0) and naloxone (Grade 1) injection sites.

Necropsy

Terminal procedures as well as collection and microscopical examination of tissues were illustrated in the following tables (from the Applicant's submission):

Text Table 7
Terminal Procedures

Group Number	Number of Animals Males	Scheduled Euthanasia Day	Necropsy Procedures Necropsy	Necropsy Procedures Tissue Collection	Histology Processing	Microscopic Evaluation
1	3	4	X	Select Tissues[a]	Select Tissues[a]	Select Tissues[a]

X = Procedure conducted.
Histology Processing = trimmed, embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.
[a] See Text Table 8 for list of tissues applicable to each procedure.

Text Table 8
Tissue Collection and Preservation

Animal identification[a]
Muscle, skeletal (underlying muscles at injection sites)
Site(s), administration: Injection sites 1 and 2
Additional tissues as deemed necessary by macroscopic evaluation at necropsy

[a] Tissue was collected and preserved but was not histologically processed or microscopically evaluated.

All main study rabbits were euthanized (scheduled euthanasia) on Day 4 and subjected to a complete necropsy examination. The necropsy included an evaluation of the carcass and musculoskeletal system, all external surfaces and orifices, cranial cavity and external surfaces of the brain, and remaining cavities (thoracic, abdominal, and pelvic) with their associated organs and tissues.

Gross Pathology
Tissues collected for macroscopic (gross) observations were described in Applicant Tables 7 and 8 above. The following table illustrates the macroscopic findings at Day 4 (from the Applicant's submission):

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male 0/10 mg Group 1
Number of Animals:	3
LUNG	
Submitted	1
Focus, dark	1
MUSCLE, SKELETAL	
Submitted	3
No Visible Lesions	3
SITE, ADMINISTRATION, 1	
Submitted	3
No Visible Lesions	1
Focus, dark	2
SITE, ADMINISTRATION, 2	
Submitted	3
Focus, dark	3
SKIN	
Submitted	1
Scab	1

According to the Pathology Report, dark focus was observed in the subcutaneous tissue at the injection site of 25 mg/mL naloxone hydrochloride (Injection Site 2) in 2 rabbits (Animal No. 1001 and 1003). Dark focus correlated microscopically with focal and minimal to mild subcutaneous hemorrhage which was within the limits of expected normal response to needle puncture. Therefore, dark focus was considered to be a procedural-related change and unrelated to naloxone hydrochloride.

In the Pathology Report, there was no microscopic correlate for dark focus in the subcutaneous tissue and/or underlying skeletal muscle at the injection site of the sodium chloride control (Injection Site 1; Animal No. 1001 and 1002) or 25 mg/mL naloxone hydrochloride (Injection Site 2; Animal No. 1002).

According to the Pathology Report, scab observed on the left hindlimb adjacent to the sodium chloride control injection site (Injection Site 1) of 1 rabbit (Animal No. 1002) correlated microscopically with minimal serocellular crust. The scab also had associated microscopic findings including focal, minimal epidermal hyperplasia and minimal parakeratotic hyperkeratosis. This finding was considered incidental and expected to occur occasionally from the hair clipping procedure. Therefore, it was considered unrelated to administration of naloxone hydrochloride.

Thus, these gross findings do not appear to be treatment-related and there were no further treatment-related changes in gross pathology in this study.

Histopathology
Tissues collected for microscopic examination were described in Applicant Tables 7 and 8 above. The following table illustrates the microscopic findings on Day 4 (from the Applicant's submission):

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male 0/10 mg Group 1
Number of Animals:	3
LUNG	
Examined	1
No Visible Lesions	1
MUSCLE, SKELETAL	
Examined	3
Degeneration/necrosis; myofiber	3
.... minimal	3
SITE, ADMINISTRATION, 1	
Examined	3
No Visible Lesions	2
Infiltration, mononuclear cell; subcutaneous tissue	1
.... minimal	1
SITE, ADMINISTRATION, 2	
Examined	3
No Visible Lesions	1
Degeneration/necrosis; fascia	1
.... mild	1
Hemorrhage; subcutaneous tissue	2
.... minimal	1
.... mild	1
Infiltration, mononuclear cell; subcutaneous tissue	1
.... minimal	1
SKIN	
Examined	1
Crust; serocellular	1
.... minimal	1

In the Pathology Report, microscopic findings observed at both the control and test article sites (Injection Sites 1 and 2, respectively) and underlying skeletal muscles were of similar severity and/or incidence and within the limits of the expected responses to needle puncture (Sellers et al., 2020). These included focal and minimal to mild myofiber degeneration/necrosis with associated minimal histiocyte infiltration, minimal mononuclear subcutaneous infiltration, and minimal to mild subcutaneous hemorrhage.

Conclusions
A total of 3 male New Zealand White rabbits were each given saline control in Injection Site 1 and naloxone 10 mg in Injection Site 2 (intramuscular injection in the right and left quadriceps muscle, respectively) on Day 1 and were observed on Day 1 post dose to the scheduled sacrifice on Day 4. All rabbits survived to the scheduled euthanasia on Day 4. There were no treatment-related changes in clinical observations and body weight.

Dermal scoring demonstrated Grade 0 erythema and edema at both the control and naloxone injection sites in all 3 rabbits with an increase to Grade 1 edema in the naloxone injection site in 1/3 rabbits.

Gross changes at the injection sites (dark focus) and adjacent skin (scab) were considered related to the dosing procedure and not treatment related. Microscopic changes at the injection sites (monocellular cell infiltration and hemorrhage of the subcutaneous tissue as well as degeneration/necrosis of the fascia), skin (serocellular crust), and skeletal muscle (degeneration/necrosis of the myofiber) were considered expected responses to needle puncture and not considered either dose limiting or unacceptable for the proposed indication.

Juvenile Animal Study
The Applicant has not conducted a juvenile animal study to support the higher naloxone 10 mg dose and 25 mg/mL concentration. However, in an agreed upon pediatric study plan (PSP), the Applicant has committed to conducting a juvenile animal study as a postmarketing requirement to support dosing in pediatric subjects 12 years and younger but will depend on PK/PD modeling demonstrating that the predicted naloxone exposure information with this product results in higher systemic levels than the referenced product. The Applicant identified the central nervous system, endocrine, and reproductive systems as the most sensitive target organs vulnerable to toxicological insult in the proposed pediatric age range of 0 to 12 years of age based on literature results. A protocol for the proposed juvenile animal study in rats will be submitted to the Division for review prior to initiating the study.

11 Integrated Summary and Safety Evaluation

The Applicant submitted a local intramuscular tolerance study in rabbits, an extractables and leachables assessment, and an elemental impurities assessment in support of this marketing NDA. The proposed naloxone drug formulation does not contain any novel excipients. The specifications as proposed for drug substance impurities meet ICH Q3A(R2) qualification thresholds. The specifications proposed for the drug product degradants meet Q3B(R2) qualification thresholds with the exception of (b) (4) (b) (4) Three unidentified drug product degradants with specifications below the qualification threshold but above the identification threshold will be identified postmarketing (see quality review). The specification (b) (4) exceeds the ICH Q3B qualification threshold. However, based on the benefit:risk for this potentially

life-saving medication, definitive qualification studies can be completed postmarketing at the discretion of the clinical team.

The proposed container closure used in the proposed drug product is the same container closure used for the lower strength EVZIO products. An extractables and leachables assessment was performed on the proposed container closure. The analytical evaluation threshold (AET) was appropriately determined. A controlled extractable study was performed on the primary container components (glass cartridge, rubber stopper, and rubber cap). These components underwent extraction and analyzed for volatile, semi-volatile, non-volatile, and elemental extractable compounds. Based on the extractable compounds identified, a leachable compound screening was performed. The leachable compounds identified (b) (4) were below the 5 mcg/day threshold at the maximum daily dose. These data obtained with the higher naloxone concentration are comparable to the leachable profile obtained for the lower strength naloxone products that also showed no leachable compounds above the 5 mcg/day qualification threshold at multiple timepoints during stability. There are no safety concerns or issues for the container closure system.

The elemental impurities assessment indicates that all appropriate elemental impurities were evaluated and determined to be below the ICH Q3D permissible limits with the exception of (b) (4) Acceptable limits for (b) (4) ((b) (4) mcg/day at the maximum daily dose, respectively) were determined from dietary intakes and application of a 10x safety factor taking into consideration the difference in oral and intramuscular routes of administration for these elementals ((b) (4) mg/day (b) (4) and (b) (4) mg/day (b) (4)) and bioavailability. As such, the elemental impurities assessment is acceptable.

In an intramuscular local tolerance study in rabbits, a total of 3 male New Zealand White rabbits were each injected with saline control in Injection Site 1 and naloxone 10 mg in Injection Site 2 (intramuscular injection in the right and left quadriceps muscle, respectively) on Day 1 and were observed on Day 1 post-dose to the scheduled sacrifice on Day 4. All rabbits survived to the scheduled euthanasia on Day 4. There were no treatment-related changes in clinical observations and body weight. Dermal scoring demonstrated Grade 0 erythema and edema at both the control and naloxone injection sites in all 3 rabbits with an increase to Grade 1 edema in the naloxone injection site in 1/3 rabbits. Gross changes at the injection sites (dark focus) and adjacent skin (scab) were considered related to the dosing procedure and not drug treatment-related. Microscopic changes at the injection sites (monocellular cell infiltration and hemorrhage of the subcutaneous tissue as well as degeneration/necrosis of the fascia), skin (serocellular crust), and skeletal muscle (degeneration/necrosis of the myofiber) were considered expected responses to needle puncture and not dose limiting. The above study did not test the local tissue toxicity of a SC injection. It is noted that the needle length for this device is approximately 0.5 inches (13 mm). The local response after IM injection suggests minimal concern, particularly given the risk:benefit

for this potentially life-saving therapy. The existing human PK data also provides some degree of characterization of the local tissue response to this drug product.

12 Appendix/Attachments

References

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