CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208969Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Resubmission (class 2)
Application Number(s)	208969
Priority or Standard	Standard
Submit Date(s)	September 7, 2022
Received Date(s)	September 7, 2022
PDUFA Goal Date	March 7, 2023
Division/Office	DAAP
Reviewer Name(s)	Corinne Ahmar, MD
Review Completion Date	March 6, 2023
Established/Proper Name	Naloxone Hydrochloride
(Proposed) Trade Name	
Applicant	Amphastar
Dosage Form(s)	Intranasal, Drug-device combination
Applicant Proposed Dosing Regimen(s)	4mg/0.25 ml per intranasal administration
Applicant Proposed Indication(s)/Population(s)	For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression (as included in the proposed label).
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adults and pediatric patients.

Clinical Review
Corinne Ahmar, MD
NDA 208969
Naloxone Hydrochloride nasal spray 4 mg/0.25 ml

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Glossary

This glossary should include all acronyms used in your review. The sample list below includes commonly used acronyms and may be used as a starting point.

AC	advisory committee
AE	adverse event
AR	adverse reaction
AV	atrioventricular
BA	bioavailability
BRF	Benefit Risk Framework
CBC	complete blood count
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMP	comprehensive metabolic profile
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DPMH	Division of Pediatric and Maternal Health
ECG	electrocardiogram
eCTD	electronic common technical document
EOS	end of study
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
Hcl	Hydrochloride
Hgb	hemoglobin
IAF	investigator assessment findings
ICH	International Council for Harmonization

IM	intramuscular
IN	intranasal
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MPD	minor protocol deviation
Msec	millisecond
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NOME	nasal and oropharyngeal mucosa exam
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PPP	per protocol population
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneously
SOC	system organ class
SPD	severe protocol deviation
SSA	symptom Self-Assessment
Study A3	Study API-N002-CL-A3
Study A4	Study API-N002-CL-A4
TEAE	treatment emergent adverse event
Wbc	white blood cell count

1. Executive Summary

1.1. Product Introduction

Naloxone hydrochloride is an opioid antagonist that has been marketed since 1971 for the reversal of opioid overdose, as manifested by respiratory and/or central nervous system depression. Amphastar developed Naloxone Hydrochloride Nasal Spray as a combination drug-device product for the emergency treatment of known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression, and submitted the application under Section 505(b)(2) of the Food, Drug, and Cosmetics Act (FD&C Act) with reliance on the Agency's previous findings of safety and effectiveness for the listed drug Narcan injection (naloxone hydrochloride 0.4 mg, NDA 16636). Naloxone Hydrochloride Nasal Spray is a single-use intranasal (IN) spray that delivers 4 mg of naloxone hydrochloride (HCl) via a nasal spray device. Naloxone Hydrochloride Nasal Spray is intended for out-of-hospital use to reverse opioid overdose and it is designed for a caregiver or untrained layperson to administer naloxone in the event of an opioid overdose.

Amphastar had initially submitted this application on April 19, 2016. It received a complete response from our Division due to several deficiencies, including (b) (4) that was inadequate for use in the younger pediatric population. The application was resubmitted following multiple modifications, including, but not limited to (b) (4) dose (4 mg (b) (4) a (b) (4) volume of intranasal administration (0.25 ml (b) (4) and a modified administration device.

Given that this is a resubmission, this review is also based on the initial review by Dr. Jen Nadel, dated January 11, 2017.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant conducted a bioavailability/comparability study demonstrating comparable (or higher) plasma concentration between Naloxone Hydrochloride Nasal Spray, and the reference listed drug (Narcan® NDA 016636) in adults. Because the proposed product has a volume of 0.25 ml and the reference listed drug a volume of 0.1 ml, the Agency required the Applicant to provide support for the volume of their modified product in pediatric patients including infants, given that no drug with such IN administration volume has been approved for patients younger than 3 years of age, and given the concern that a volume too large could lead to product run off in the posterior pharynx which could cause aspiration and/or loss of efficacy. The Applicant provided a retrospective observational pediatric study and a modeling study followed by an additional simulation study and a sensitivity analysis at the Agency's request. Based on the review of these studies and on the extensive discussions with the pediatric and the clinical pharmacology teams, as well as the previous findings of effectiveness of Narcan, I conclude that the safety and efficacy of Naloxone Hydrochloride Nasal Spray for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and in children of all ages down to birth is adequately supported by the data submitted.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Naloxone is a nonselective short-acting pure opioid antagonist that has a high affinity to opioid receptors. It displaces opioids at their receptor sites to reverse the potentially fatal respiratory depression induced by opioids, and prevent hypoxia associated with injury and death.

Opioid overdose can occur by accidental exposure in children or in adults, or through intentional misuse and abuse, leading to tens of thousands deaths in the United States every year. The fatalities and hypoxia-associated injury following an opioid overdose can be prevented by timely administration of naloxone.

Currently several naloxone products, including generics, are approved in the United States for use in the community to reverse opioid overdoses in adults and pediatric patients.

The addition of another naloxone product designed to be used by anyone including an untrained caregiver, to the available armamentarium, can contribute in tackling the public health crisis associated with opioid overdoses.

The efficacy of Naloxone Hydrochloride Nasal Spray is supported by one comparative bioavailability PK study demonstrating a naloxone exposure exceeding the plasma concentration of the reference product but staying within the exposures achieved with the initial approved dose range of the reference product (0.4 to 2 mg IV).

Naloxone Hydrochloride Nasal Spray has a larger volume of administration than approved IN naloxone products (0.25 ml compared to 0.1 ml). The Applicant submitted adequate data supporting its use in adults as well as children.

The main risks of naloxone products are severe precipitated opioid withdrawal and its associated cardiovascular risks. In post-operative settings, reversal of opioid depression with naloxone may lead to tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest, primarily in patients with pre-existing cardiovascular disorders or on concomitant drugs that may have similar adverse cardiovascular effects. In neonates, opioid withdrawal may be life-threatening if not properly treated.

The safety profile of Naloxone Hydrochloride Nasal Spray is acceptable. The risk of acute opioid withdrawal is outweighed by the benefit of reversing a life-threatening opioid overdose. Relying on the evidence of efficacy and safety submitted, I recommend approval of Naloxone Hydrochloride Nasal Spray for the emergency treatment of known or suspected opioid overdose in adults and children.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Known or suspected opioid overdose is characterized by life-threatening respiratory and central nervous system depression that may lead to death or irreversible hypoxic injury. Opioid overdose related fatalities remain high. Overdose can occur by accidental exposure in children or in adults, or through intentional misuse and abuse.	Opioid overdose is a life-threatening condition that contributes to a significant number of deaths.
Current Treatment Options	• Several naloxone products are available for the treatment of opioid overdose, including generics. Three available products are approved under an NDA: • Narcan® Nasal Spray (naloxone hydrochloride; NDA 208411) approved on November 18, 2015, consists of a single-dose device of 2 mg and 4 mg doses. • Kloxxado® nasal spray (naloxone hydrochloride; NDA 212045) approved on April 29, 2021, consists of a single-dose device of 8 mg dose. • ZIMHI® (naloxone hydrochloride; NDA 212854) approved on October 15, 2021, consists of a single-dose intramuscular or subcutaneous auto-injector device for a 5 mg dose. • The duration of action of these products is shorter than the duration of action of most opioids, hence the need for continued monitoring after administration, with a potential need for multiple naloxone administrations. • The safety profile of these products is acceptable.	Naloxone Hydrochloride Nasal Spray would add another product to the available armamentarium to tackle the public health crisis associated with opioid overdoses
Benefit	• The efficacy of Naloxone Hydrochloride Nasal Spray is supported by the comparative bioavailability PK study demonstrating a naloxone exposure exceeding plasma concentration of reference product. • Naloxone Hydrochloride Nasal Spray has a larger volume of administration than approved IN naloxone products (0.25 ml compared to 0.1 ml). There were initial concerns that with such a volume, part of the administered product would be	The available data provides substantial evidence to support the effectiveness of Naloxone Hydrochloride nasal spray for adult and pediatric populations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	lost to runoff in the posterior pharynx and consequently a lower efficacy particularly in young pediatric populations such as infants. Amphastar submitted modeling and simulations studies (discussed further in this review) showing a minimal volume of runoff including in the youngest pediatric patient (as young as neonates).	
Risk and Risk Management	• The most frequent adverse event reported in the submitted studies with Naloxone Hydrochloride nasal spray was headache. Dizziness, lightheadedness, paresthesia oral, dry throat, dysuria, leg infection, pregnancy, migraine, and vomiting were reported as well. All adverse events were mild to moderate in severity. There were no deaths, serious adverse events, or severe adverse events. • Local safety/toxicity assessments reported in the submitted studies did not raise any significant concern. • Approved naloxone labels have several warnings for safety concerns, including the risk of recurrent respiratory and/or central nervous system depression after an initial improvement due to the shorter duration of action of naloxone, the risk of limited efficacy with partial agonists or mixed agonist/antagonists, and the risk of precipitation of severe opioid withdrawal in patients who are opioid-dependent. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. • Delay or inadequate exposure of Naloxone are life-threatening and may lead to death or permanent disabilities.	There are no new safety concerns with the use of Naloxone Hydrochloride nasal spray when used for the labeled indication. There is no need for risk mitigation beyond the information provided in the labeling.

2. Therapeutic Context

2.1. Analysis of Condition

The opioid crisis was declared a public health emergency (Opioid PHE) in 2017. More than 80,000 people died of opioid-involved overdose deaths in the 12-month period ending in January 2022, representing 75 percent of all drug overdose deaths. Naloxone is a critical tool to help reduce opioid overdose deaths and address this public health crisis. Opioid overdose is characterized by life threatening respiratory and central nervous system (CNS) depression that, if not immediately treated, may lead to significant morbidity and mortality. Naloxone reverses the effects of respiratory depression and sedation by displacing opioids from the mu-opioid receptor in the CNS. Timely administration of naloxone, usually within minutes of the first signs of an opioid overdose, can counter the overdose effects[1].

2.2. Analysis of Current Treatment Options

Naloxone was initially approved in 1971 as an injectable formulation, under the brand name Narcan® to treat opioid overdose. Narcan® is no longer marketed; however, generics are currently available as described in the table below. These injectable products are generally intended for use in a healthcare setting.
Narcan® Nasal Spray and Evzio® inj. are specifically approved for use in the community. There are multiple Naloxone products approved including the original Narcan®, though the latter was discontinued (not for reasons of safety or effectiveness) and only its generics are available. Three approved products under an NDA are currently available: Narcan® Nasal Spray, Kloxxado® nasal spray, and ZIMHI® auto-injector.
In addition to the naloxone products, nalmefene (Revex®) injectable, another opioid antagonist, was approved by the Agency in 1995 (NDA 020459) and is indicated for the complete or partial reversal of opioid drug effects and management of known or suspected opioid overdose. Revex® was discontinued in 2014 not for reasons of safety nor effectiveness and generic versions of nalmefene are currently available on the market.

Table 1: Available and discontinued naloxone products

Naloxone Drug Product Name	NDA/ANDA	Approval Date	Dose Form
Narcan® (discontinued)	NDA 016636	04/13/1971	Injection
EVZIO® (Naloxone HCl) (discontinued)	NDA 205787	04/03/2014	Injection
EVZIO® (Naloxone HCl) (discontinued)	NDA 209862	10/19/2016	autoinjector
Narcan® Nasal Spray	NDA 208411	11/18/2015	Nasal Spray 2mg/spray, 4 mg/spray
Naloxone HCl	ANDA 209522	04/19/2019	Nasal Spray 4mg/spray
Kloxxado® (Naloxone HCl)	NDA 212045	04/29/2021	Nasal Spray 8mg/spray
ZIMHI® (Naloxone HCl)	NDA 212854	10/15/2021	IM and SC 5mg/inj
Naloxone HCl	ANDA 211951	06/21/2022	Nasal Spray 4mg/spray

Availability of Proposed Active Ingredient in the United States
There are several approved drug products containing the active ingredient naloxone in the United States (Table 1) that are approved with the same indication as Naloxone Hydrochloride Nasal Spray . Naloxone is also included as an active ingredient in several products in combination with opioid ingredients for the treatment of opioid dependence and pain. It is generally included in these products to deter abuse of the opioid component.

Known Safety Issues of Naloxone
There are several warnings on the label for naloxone regarding acute opioid withdrawal. Naloxone may cause an abrupt precipitation of opioid withdrawal. Some of the common symptoms of opioid withdrawal include agitation, anxiety, muscle aches, rhinorrhea, diaphoresis, diarrhea, vomiting, and pruritus. In neonates, withdrawal may be life-threatening. Abrupt postoperative reversal of opioids has been shown to lead to adverse cardiovascular events such as hypotension, hypertension, ventricular tachycardia, ventricular fibrillation, and pulmonary edema.
Other warnings include the risk of recurrent respiratory and/or central nervous system depression after an initial improvement due to the shorter duration of action of naloxone, hence the necessity of seeking emergency assistance immediately after administration of the first dose of naloxone and keeping the patient under continued surveillance, as well as the risk of limited efficacy with partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2: Key Pre-submission Regulatory Activity

Date	Meeting/Submission Type	Key Comments
02/10/2015	Pre-IND Meeting (PIND 124672)	• 505(b)(2) pathway appropriate • PK standards established by the Division in lieu of efficacy studies given ethical concerns associated with evaluating the efficacy of a novel naloxone product • (b) (4)
03/03/2015	New IND submitted	
03/27/2015	Fast Track designation granted	
10/13/2015	Pediatric Study Plan agreement	

11/5/2015	Type B Pre-NDA Meeting	• FDA expressed concern that [redacted] for pediatrics. • HF validation study showed failures that may impact efficacy of product. • Co-packing two dosing units is planned.
01/12/2016	Rolling Review granted	
04/19/2016	**New NDA submitted (initial)**	
02/17/2017	Complete response	• FDA continued to express concern (efficacy and safety) over the proposed [redacted] for young pediatric patients. • Human Factors validation study showed failures/use errors [redacted] that may impact efficacy of product. • [redacted]. • Reliability specification at expiry of [redacted]% deemed unacceptable.
05/15/2017	Type A meeting	
11/28/2017	Type A meeting	• New dose proposed: 4 mg [redacted] • New volume: 0.25 ml. Literature submitted describing pediatric patients receiving IN volumes > 0.25 mL in hospital settings. FDA requested safety information related to the administration of higher IN volume in pediatric patients in the above study. • New pre-assembled device design [redacted] • Discussion/advice re: reliability study • Discussion re: [redacted] head position [redacted] for the clinical study design.
03/18/2020	Type C meeting	• 3 analyses on pediatric safety & efficacy of the 0.25 mL volume submitted. Applicantagreed to provide additional modeling, demographic data, and include caregivers of infants in their HF study. • Pre-assembled device addresses FDA's previous concerns, new issues/comments expressed by CDRH. • FDA recommends additional PK sampling timepoints before 5 min. in the BA study. • Justification for the 2-minutes infusion time of iv comparator requested.
02/18/2021	New protocol for study A3 submitted to the IND	
05/12/2021	New protocol for study A4 submitted to the IND	
09/07/2022	**NDA Resubmission (class 2)**	

3.3. Foreign Regulatory Actions and Marketing History

There were no significant foreign market developments for this product.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed at the clinical site (West Coast Clinical Trials (WCCT) Global, Inc. 5630 Cerritos Avenue, Cypress, CA) nor at the analytical site (Amphastar Pharmaceuticals, Inc. Research and Development Department, 11570) since a recent inspection was conducted for the sites listed.

4.2. Product Quality

A pre-approval inspection of the device facility was recently conducted, and the facility was found to be acceptable. No chemistry / manufacturing concerns were found. Please refer to the CMC (chemistry, manufacturing, and controls) review for more details.

4.3. Clinical Microbiology

No concerns were identified from a microbiology perspective. Please refer to the CMC (chemistry, manufacturing, and controls) review by Dr. Valerie Amspacher for more details.

4.4. Nonclinical Pharmacology/Toxicology

Nno pharmacology /toxicology findings or concerns related to the safety or effectiveness of this product were found. Please see the pharmacology toxicology review by Dr. Carlic Huynh for details.

4.5. Clinical Pharmacology

The Applicant conducted a comparative bioavailability study (study A3) in support of the Naloxone 4 mg nasal spray, which is the only formulation proposed for marketing in this application.
The conclusion reached by the clinical pharmacology reviewer is that Naloxone exposure in this study exceeded the plasma concentration of the reference product (0.4 mg IM injection) and these higher plasma levels were achieved in the early critical period (2-10 minutes)."
For more details, please refer to the clinical pharmacology review by Dr. Srikanth Nallani, PhD.

4.6. Devices and Companion Diagnostic Issues

The final review from CDRH (Center for Devices and Radiological Health) is pending at the time of this review. Please refer to the CDRH review by Dr. Kyran Gibson for details.

4.7. Consumer study reviews

DMEPA (the Division of Medication Error Prevention and Analysis) evaluated the human factors validation study results submitted by Amphastar Pharmaceuticals and determined that additional labeling mitigations could be implemented to address use errors that occurred with critical tasks. DMEPA provided recommendations for Amphastar Pharmaceuticals and determined that additional human factors validation

testing data is not needed at this time. Please refer to the review by Dr. Damon Birkemeier from DMEPA for details.

5. Sources of Clinical Data and Review Strategy

Since this application was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetics Act (FD&C Act), a formal efficacy study was not required. Amphastar conducted 2 clinical studies, Study API-N002-CL-A3 (referenced throughout this review as study A3) and API-N002-CL-A4 (referenced throughout this review as study A4), to support their application.

Study A3 is a PK/comparability study conducted to evaluate the bioavailability, safety, and tolerability of Naloxone Hydrochloride Nasal Spray 4 mg and 10 mg compared with Naloxone 0.4mg IM and 2mg IV. The PK study analysis was reviewed by the clinical pharmacology team and I reviewed its safety data.

I also reviewed Study A4 that evaluated the effect of Naloxone Hydrochloride Nasal Spray 4 mg on Olfactory Function.

A retrospective observational pediatric study (Study C) was reviewed by me concurrently with Dr. Ndidi Nwokorie from DPMH/pediatrics.

A modeling study assessing the nasal Spray Run-Off Volumes in Neonate and Pediatric Nasal Airways by Computational Fluid Dynamics Simulations was reviewed by Dr. Zhihua Li from the Division of Applied Regulatory Sciences (DARS).

5.1. Table 3: Summary of Clinical Studies

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Objectives	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	Controlled Studies to Support Efficacy and Safety							
API-N002-CL-A3 (study A3)	Randomized, Evaluator-blinded, Four Treatments, Crossover	Single Dose Naloxone Intranasal, IM, IV.	Evaluate the PK, tolerability, and safety of the drug product	***AUC0-t****, (where t*= of Treatment C3)	4 single doses of Naloxone (IN, IM, or IV), each randomly assigned to 1 of the 4 dosing periods separated by 3 to 14 days. Follow up phone call 1-7 days after Visit-4 or study termination	32	Healthy adult volunteers	Single center in Cypress, CA, USA (WCCT Global, Inc.)
	Studies to Support Safety							
API-N002-CL-A4 (study A4)	Randomized, Double-blinded, Two Treatments, Crossover	Single dose Intranasal Naloxone, 10mg in 0.25 ml	Effect on olfactory function	Olfactory Performance change from baseline	Two single doses of Naloxone (IN and IV), each randomly assigned to 1 of the 2 dosing visits separated by 3 to 14 days. Follow up phone call 1-7 days after completion of Visit-2 or study termination.	28	Healthy adult volunteers	Single center in North Dartmouth, MA, USA (Northeast Medical Research Associates, Inc)

API-N002-CL-C (Study C)	Retrospective Observational	Mostly single dose (rarely 2 doses) Intranasal medication(s)	Safety of IN delivery volume in young children	AE related to IN dosing, more particularly any ADE defined as respiratory compromise (e.g., aspiration) resulting from IN drug delivery.	NA	668 (PPP 571 after exclusion of cases <0.25 ml	Children ≤ 3 years of age	Four medical centers in the USA
	Other studies pertinent to the review of efficacy or safety: modeling study							
Modeling of nasal spray run-off volumes in neonate and pediatric nasal airways (≤ 3 years of age) by physiology-based, computational fluid dynamics simulations.					NA	NA	NA	

6. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant submitted the application under Section 505(b)(2) of the Food, Drug, and Cosmetics Act (FD&C Act) with reliance on the Agency's previous findings of safety and effectiveness for the listed drug Narcan® (NDA 016636).
No new efficacy studies were required to support this application. Therefore, the Applicant's development program consisted of demonstrating comparable or greater systemic exposure to naloxone with their new naloxone product, particularly in the early critical period after drug administration.

6.1. Study API-N002-CL-A3

6.1.1 Study design and conduct

This study was a randomized, evaluator-blinded, single-dose, four-treatment, four-period, crossover, fasting study, comparing the pharmacokinetic (PK) and tolerability of Naloxone Hydrochloride Nasal Spray 4mg/0.25 ml and Naloxone Hydrochloride Nasal Spray 10mg/0.25ml, with Intravenous and Intramuscular Naloxone in 32 healthy women and men volunteers between the age of 18 and 45.
The screening visit (3-21 days prior to Visit-1) was followed by four dosing visits (Visit-1 through Visit-4, separated by a 3–14-day period), and a follow up phone evaluation (1-7 days after the completion of Visit-4). Visit 4 is the End-of-study (EOS) visit. The screening visit included a "dry run" (IN administration of 1 ml of NS as placebo). Subjects may be excluded from the study if they show substantial discomfort during the dry run. Treatments V1 (Naloxone Hydrochloride Nasal Spray 4 mg) and V2 (Naloxone Hydrochloride Nasal Spray 10 mg) were administered by the IN route, Treatment C3 (Naloxone hydrochloride 0.4 mg inj.) was delivered by IM injection, and Treatment C4 (Naloxone Hydrochloride 2 mg inj.) was administered by slow IV infusion over 2 minutes. Blood samples were collected for PK throughout the study.

Safety and tolerability assessments including Nasal cavity and oropharyngeal examinations were performed as described in section 8.1 of the review.

Table 4 Study A3 Treatment arms

Study Arms	V1	V2	C3	C4
Products				
Drug Formulation Code*	**N002-16-0.25**	**N002-40-0.25**	**Comparator**	**Comparator**
Manufacturer	IMS	IMS	Hospira (ANDA 070256)	IMS (ANDA 072076)
Naloxone Concentration (mg/mL)	16	40	0.4	1
Fill Volume, mL	0.25	0.25	1	2
Delivery				
Delivery Route	IN	IN	IM	IV
# of Nostrils for IN	1	1	-	-

Total volume delivered (mL)	0.25	0.25	1	2
Total Naloxone Dose (mg)	**4**	**10**	**0.4**	**2**

* Formulation code: Concentration (mg/mL) and fill volume (mL). **N002:** Naloxone Hydrochloride Nasal Spray. Blue-shaded column: the to-be-marketed dose, volume, and concentration.

A/ Study Endpoints

The PK profile of Naloxone Hydrochloride Nasal Spray was analyzed for the Per-Protocol Population (PPP), defined as subjects who had evaluable IM and IV Naloxone (Treatment-C3/-C4), and at least one evaluable visit of two (2) Naloxone Hydrochloride Nasal Spray treatments (Treatment-V1, or -V2), and a valid number of PK blood samples collected at specified time points.

- **Primary PK endpoints**

- AUC0-t*, (t*= IM tmax of Treatment C3), defined as the partial area under the curve (AUC) in the plot of plasma Naloxone concentration versus time from time 0 to the tmax of Naloxone delivered by IM of Treatment C3.
- t', defined as the time at which the plasma Naloxone concentration of a given IN treatment first reaches the peak plasma Naloxone concentration (Cmax) of the IM
treatment.

- **Secondary Endpoints**

- Cmax, defined as the peak plasma Naloxone concentration.
- *t*max, defined as the time, at which the peak plasma Naloxone concentration (Cmax) is observed.
- *AUC0-∞*, defined as AUC in the plot of plasma Naloxone concentrations versus time from time 0 to infinity.
- *AUC0-6hrs*, defined as AUC in the plot of plasma Naloxone concentrations versus time from time 0 to the last sampling point.
- *CIN (t*)*, defined as naloxone concentrations of IN delivery at the *tmax* of IM of Treatment C3.

- **Additional Evaluations**

- Relative bioavailability of IN Naloxone treatments versus IM and IV Naloxone.

B/ Statistical Analysis Plan

- Bioequivalence (BE) Methodologies were used for PK parameter evaluations:
  - The 90% confidence interval (CI) for the geometric mean of the ratio of IN to IM or IV was used.
  - For AUC0-t*, and CIN(t*) the lower limit of 90% CI (vs. IM) should be greater than 80%.
  - For tmax and t' (vs. IM), Cmax, AUC0-6hrs, and AUC0-∞ (vs. IV), the upper limit of 90% CI should be less than 125%.
- Tolerability Evaluations:

NOME (Nasal and Oropharyngeal Mucosa Exam) scores were calculated and tabulated for all treatments at different time points; the frequency counts of subjects within each category of IAF (Investigator Assessment Findings) and SSA (Symptom Self-Assessment) data were calculated and tabulated per treatment.

C/ Protocol Amendments

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Following the Agency's complete response in 2017, the Applicant proposed a new naloxone formulation (b) (4) (4 mg/0.25 ml (b) (4) This new formulation was to be evaluated in the proposed PK study submitted to their IND on 05/12/2021. (b) (4) an IR was sent recommending that the Applicant evaluates for any olfactory function change in study subjects, to which the Applicant responded with a new proposed protocol/study (study A4) for that purpose. See section 8.2.2 for details on study A4.

6.1.2 **Study Results**

Compliance with Good Clinical Practices

The Applicant has included a statement certifying that this trial was undertaken in accordance with the current ICH Good Clinical Practice (GCP) guidelines and the current version of the Declaration of Helsinki of the World Medical Association to assure that the rights, safety, and well-being of the study subjects are protected.

Financial Disclosure

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. One investigator was listed in study A3.

Patient Disposition

A total of 32 subjects were enrolled and randomized in study A3. The numbers of evaluable subjects were 25, 24, 27, and 26 for treatments V1 (Naloxone Hydrochloride Nasal Spray 4 mg/0.25 ml), V2 (Naloxone Hydrochloride Nasal Spray 10 mg/0.25 ml), C3 (Naloxone hydrochloride 0.4 mg IM), and C4 (Naloxone Hydrochloride 2 mg IV), respectively. The evaluable population was 27.

Protocol Violations/Deviations

A total of 48 protocol deviations (7 for V1, 16 for V2, 7 for C3, 17 for C4, and one deviation during study follow-up) were documented throughout the study period, including: 16 severe protocol deviations (SPD), and 32 minor protocol deviations (MPD). All 16 SPDs were related to PK sample collected out of time window, overlapping with the subsequent PK time point(s). There were 32 minor deviations that occurred regarding (i) sampling time window, (ii) PK sample not collected, (iii) study drug leakage, and (iv) missed procedures. Please refer to the Clinical Pharmacology review by Dr. Nallani for more information on protocol deviations.

Demographic Characteristics

As described in the table below, data was obtained from young healthy volunteers between the age of 18 and 45. The study population is suitable to provide quality data that can be generalized to the target population. Please see the clinical pharmacology review for a discussion on the adequacy of the population studied for the purpose of establishing a scientific bridge to Narcan injection.

Table 5 - Demographic Profile in Treated Population

Items	V1	V2	C3	C4
Study Drugs	N002-16-0.25	N002-40-0.25	Naloxone HCl (ANDA 070256)	Naloxone HCl (ANDA 072076)
Delivery Route	IN	IN	IM	IV
Dose, mg	4	10	0.4	2
Volume, mL	0.25	0.25	1	2
Targeted # of Subjects, N # of Subjects Randomized, n1*	24 32 (12, 20)			
# of Subjects Treated, n2	27 (11, 16)	27 (11, 16)	28 (12, 16)	30 (12, 18)
# of Subjects, Evaluable, n3trt	25 (11, 14)	24 (11, 13)	27 (12, 15)	26 (12, 14)
# of Subjects, PPP-C3, n4trt3	25 (11, 14)	24 (11, 13)	27 (12, 15)	-
# of Subjects, PPP-C4, n4trt4	24 (11, 13)	23 (11, 12)	-	26 (12, 14)
Age (yr), mean ± std.	30.3 ± 6.8	29.9 ± 6.8	30.2 ± 6.7	29.9 ± 6.6
Age (yr), median (range)	30(18, 43)	29(18, 43)	30(18, 43)	29(18, 43)
Weight (kg), mean ± std.	74.1 ± 15.0	73.1 ± 13.5	74.4 ± 14.8	73.8 ± 14.0
Height (cm), mean ± std.	170.5 ± 10.2	170.4 ± 10.0	171.1 ± 9.9	171.6 ± 9.6
Race Group, N (%)				
White	10(37.0%)	10(37.0%)	10(35.7%)	10(33.3%)
Black or African-American	14(51.9%)	13(48.1%)	14(50.0%)	16(53.3%)
Asian	1 (3.7%)	1 (3.7%)	1 (3.6%)	1 (3.3%)
Others	2 (7.4%)	3 (11.1%)	2 (10.7%)	3 (10.0%)
Ethnicity, N (%)				
Hispanic	5(18.5%)	5(18.5%)	4(14.3%)	4(13.3%)
Non-Hispanic	22(81.5%)	22(81.5%)	24(85.7%)	26(86.7%)

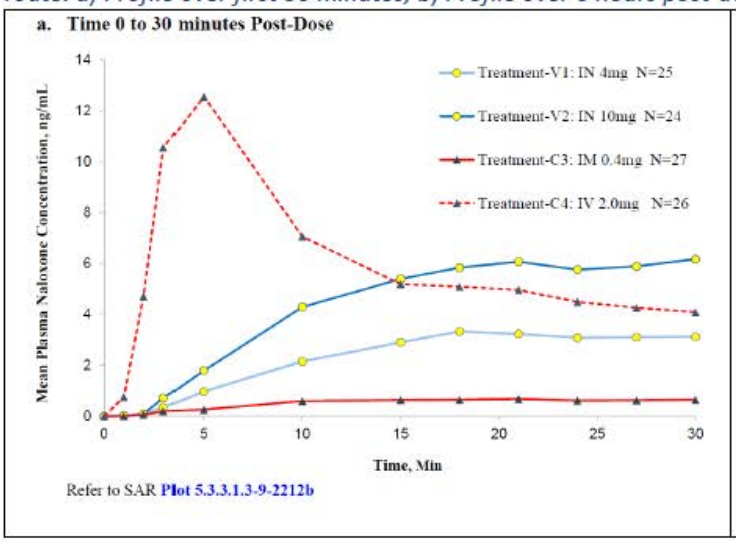
* N is provided in the format N(M, F)=Number of Subjects (Number of male, female subjects)
N002-16-0.25: Naloxone Hydrochloride Nasal Spray, concentration of 16 mg/ml, volume of 0.25 ml.
N002-40-0.25: Naloxone Hydrochloride Nasal Spray, concentration of 40 mg/ml, volume of 0.25 ml.

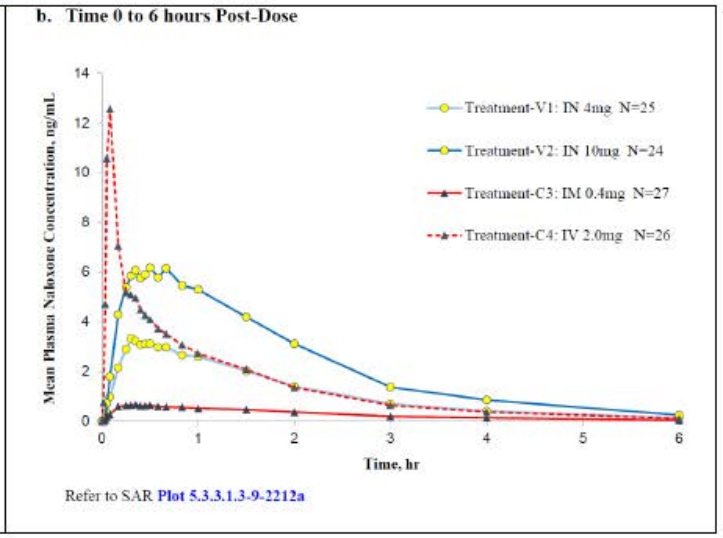
Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
There were no other baseline characteristics applicable in this study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Not applicable.

Efficacy Results – Primary Endpoint
As seen in the figure below, Naloxone exposure in this study exceeded the plasma concentration of the reference product (0.4 mg IM injection) and these higher plasma levels were achieved in the early critical period (2-10 minutes). Please refer to the clinical pharmacology review for additional details.

Figure 1: PK profile of naloxone following administration of different treatments via intranasal, intramuscular or intravenous route. a) Profile over first 30 minutes; b) Profile over 6 hours post-dose.





Data Quality and Integrity
Not applicable.

Efficacy Results – Secondary and other relevant endpoints
Not applicable.

Dose/Dose Response
Not applicable**.**

Durability of Response
Not applicable.

Persistence of Effect
Not applicable.

Additional Analyses Conducted on the Individual Trial
Not applicable.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable since only one PK study was conducted in this submission.

7.2. Additional Efficacy considerations

7.2.1. Considerations on Benefit in the Post market Setting

Not applicable

7.2.2. Other Relevant Benefits

Not applicable

7.3. Integrated Assessment of Effectiveness.

The Applicant's clinical program consists of one PK study, study API-N002-CL-A3, comparing the pharmacokinetic (PK) of naloxone nasal spray 4 mg/0.25ml with naloxone nasal spray 10 mg, naloxone 0.4mg IM, and naloxone 2mg IV, to establish a scientific bridge to the efficacy and safety findings of Narcan injection for the proposed indication.
As seen in the figures in 6.1.2, Naloxone Hydrochloride Nasal Spray 4mg in 0.25 ml was found to have a lower systemic exposure than the IV comparator and a higher systemic exposure than the IM comparator including during the early absorption phase. The study met the pharmacokinetic requirements set forth by the Division.

While the PK study showed that Naloxone Hydrochloride Nasal Spray met the criteria to rely on the Agency's previous findings of effectiveness of Narcan, the review identified deficiencies with the product. The Division had previously discussed in meetings with the Applicant our concern (b) (4) could lead to a partial absorption of the Naloxone Hydrochloride Nasal Spray dose and hence a loss of efficacy. The Applicant (b) (4) submitted a retrospective observational pediatric study analyzing 571 patient encounters from electronic medical records of pediatric patients aged 0-3 who have received medications administered intranasally (IN) at volumes of 0.25ml or more and reviewed any safety event related to IN administration such as aspiration. This study was reviewed concurrently with the pediatrics team from DPMH. For a detailed description of this retrospective pediatric study and a discussion on its results pertaining to safety, please see section 8.6.The Applicant argues (b) (4)
We did not agree with Amphastar regarding this conclusion. (b) (4) Consequently, the extent of the run-off following a 0.25 ml IN administration of Naloxone Hydrochloride Nasal Spray, and hence its efficacy, still needed to be confirmed. To that effect, the Agency had previously (in 2020) commented on modeling studies provided by the Applicant to evaluate the extent of run-off and recommended additional simulation

studies with a composite of multiple scans of patients (0-3 years old with a focus on patients 0-1 years old) to confirm that the runoff volume estimates are representative of the age range being analyzed.
Amphastar submitted a new simulation study with the requested modifications (the number of pediatric models was expanded to six, with five of them younger than 1 year old). This was reviewed by our colleagues from DARS who concluded that the new study addressed DARS's original concern. However, due to an approximate difference of 30% between the Applicant's predicted run-off fraction for the 0.5 ml volume and the run-off fraction of 0.5 ml found in the literature[3] (Hosseini et al.), DARS recommended that the Applicant provides an assessment for the differences between their simulations and the published simulation study to increase the credibility of their model. Amphastar responded by submitting a new simulation report incorporating the parameters used in the published simulation study. The results were similar to the published study and their response was hence assessed as adequate by DARS. However, the Applicant used an airflow of 1.72 L/min (20% of estimated normal rate) in those studies. Given the wide range of variations of airflow in the subject with opioid overdose, including a possible airflow of near zero in the apneic patient, our team in concurrence with DARS requested that the Applicant evaluates runoff using a range of airflows with their current model. The Applicant responded by submitting a sensitivity analyses using the model for their product with different air flow rates (0%, 10%, 30%, and 40% of estimated normal rate). The sensitivity analysis showed little impact from these air flow rates on the run-off fraction (The highest runoff fraction was 3.9% of the total IN volume administered in the 10-day old model). Please see attachment 1, 2 and 3 for details on the modeling study, the additional modeling study using Hosseini's model, and the sensitivity analysis submitted by the Applicant.
We conclude that the Applicant has submitted adequate data demonstrating the efficacy of their product in adult and in pediatric patients of all ages down to birth.

8. Review of Safety

8.1. Safety Review Approach

The Applicant submitted a 505(b)(2) application referencing the approved drug, Narcan (NDA 016636), to support the clinical efficacy and safety of Naloxone HCl Nasal Spray in the treatment of opioid related overdose. The Applicant has submitted three clinical studies,two clinical trials and one retrospective observation pediatric study, to support the safety of their product:

(i) API-N002-CL-A3: A comparative bioavailability trial (A randomized, evaluator-blinded, single-dose, four-treatments crossover study, comparing the pharmacokinetic (PK) and tolerability of Naloxone Hydrochloride Nasal Spray with Intravenous and Intramuscular Naloxone)
(ii) API-N002-CL-A4: A Randomized, Double-blinded, Two-Treatments, Crossover olfactory function study.
(iii) API-N002-CL-C: A retrospective observational single-dose intranasal study to evaluate the safety of IN delivery of volume > 0.25 ml in young children.

I reviewed the safety information provided in these 3 studies. The pediatric study safety results were reviewed concurrently with the pediatric team from DPMH.

8.2. Review of individual trials used to support safety

8.2.1 Study API-N002-CL-A3

This is a randomized, evaluator-blinded, single-dose, four-treatment, four-period, crossover, fasting study, comparing the pharmacokinetic (PK) and tolerability of Naloxone Hydrochloride Nasal Spray 4mg/0.25 ml and Naloxone Hydrochloride Nasal Spray 10mg/0.25ml, with Intravenous and Intramuscular Naloxone in 32 healthy women and men volunteers between the age of 18 and 45 years old. Please refer to section 6.1 for additional details on the conduct of this study.

Three local safety Evaluations were conducted:

1. Nasal and Oropharyngeal Mucosa Exam (NOME) Scores: performed at baseline, 1-hr and 4-hr post-dose at each dosing visit. The NOME scores for different compartments within the nasal cavity (right nostril) and oropharyngeal passage are generated by assessing signs of edema, erythema, or appearance of lesions using a 5-point scale: 0 = None; 1 = Little; Very Mild; 2 = Mild; 3 = Moderate; 4 = Severe.
2. Subject Symptom Self-Assessment (SSA): performed at end of each study visit to rate the tolerability after study administration. SSA was graded using the same 5- point scale as the NOME, to rate the following symptoms: a) burning or pain, b) need to blow nose, c) facial pain/pressure, d) others.
3. Investigator Assessment Findings (IAF): Performed at the end of each study visit, IAF classified the above findings into the following three categories: 1. Normal; 2. Abnormal-NCS (Non-Clinically Significant); and 3. Abnormal-CS (Clinically Significant).

Systemic Safety evaluations

Vital signs, ECG, laboratory tests (Complete Blood Count (CBC), comprehensive metabolic panel and urinalysis, urine pregnancy test, urine screen for drugs and alcohol) and adverse events were monitored. Vital signs and 12 lead ECG were performed pre and post dose, lab tests and physical exam conducted at screening and at EOS, urine pregnancy test and urine screen for drugs and alcohol at screening and pre-dose at each visit.

8.2.2. Study API-N002-CL-A4

This is a randomized, Double-blinded, Single-dose, Two-treatment, Two-period, Crossover Study of Naloxone Hydrochloride Nasal Spray on Olfactory Function in Healthy Adult Volunteers.

This study's purpose was to compare the effect of a higher dose of Naloxone Hydrochloride Nasal Spray (Naloxone 10 mg in 0.25 ml) and placebo (both administered IN) on the olfactory function of 28 healthy men and women 18-45 years of age.

The study consisted of a screening visit (3-21 days prior to Visit 1), two dosing visits separated by a 3–14-day period, and a follow-up phone evaluation (1-7 days after the completion of Visit-2).

Table 6: Study Treatments Designation

Study Treatments	P	T
Products		
Drug Formulation Code*	N002-00-0.25	N002-40-0.25
Drug Product	Placebo	N002
Manufacturer	IMS	IMS
Naloxone Concentration, mg/mL	0	40
Fill Volume, mL	0.25	0.25
Delivery		
Delivery Route	IN	IN
Dose, mg	0	10
Volume by IM, mL	-	-
Volume per Nostrils, mL	**0.25**	**0.25**
# of Nostrils for IN	1	1
Total volume delivered, mL	0.25	0.25
Total Naloxone Dose	**0 mg**	**10 mg**

* Formulation code: Concentration (mg/mL) and fill volume (mL); N002: Naloxone Hydrochloride Nasal Spray
P: placebo; T: treatment

The olfactory function of study subjects was assessed using the University of Pennsylvania Smell Identification Test (UPSIT), performed at Screening, at each study visit (prior to study drug dosing), and 4 hours after intranasal administration.
Systemic safety evaluations included assessment of vital signs, ECG, laboratory tests (complete blood count, comprehensive metabolic panel, and urinalysis), and adverse events.

Table 7: Olfactory Performance Classification

Olfactory Performance Score	Olfactory Performance	UPSIT Score	
		Women	Men
1	Anosmia	< 19	< 19
2	Severe Microsmia	19-25	19-25
3	Moderate Microsmia	26-30	26-29
4	Mild Microsmia	31-34	30-33
5	Normosmia	> 34	> 33

Study Endpoint Evaluations

i. Primary Study endpoint: Olfactory Performance change from baseline.

ii. Secondary Study Endpoint: UPSIT score change from baseline

Summary of Study Results

Compliance with Good Clinical Practices

This clinical trial was undertaken in accordance with the current ICH Good Clinical Practice (GCP) guidelines as stated by the Applicant.

Patient disposition

A total of 28 subjects were enrolled and randomized. All 28 subjects received both study treatments (no failed screens and no dropouts).

Study Compliance

A total of eight (8) protocol deviations (1 in the Placebo arm, 1 in the Treatment arm, and 6 deviations occurred outside the study period) were documented throughout the study. All 8 protocol deviations were considered minor, including missed procedures, or safety assessment conducted out of time window. No missing data points were documented in the study.

Demographics

The gender profile of all treated subjects was 42.9% (12/28) male and 57.1% (16/28) female, with mean age of 31.2 ± 8.5 years old, mean body weight 75.3 ± 14.3 kg, and mean height is 168.5 ± 9.0 cm. The majority were Caucasians (82.1%), 3.6% were African Americans, 3.6% were Asian, and 17.9% were Hispanics. The study population is adequate to provide quality data that can be generalized to the target population.

Study Safety results

Please refer to section 8.5 for a description and analysis of the study safety results.

Note: the dose of Naloxone Hydrochloride Nasal Spray used in this study is 10 mg with a concentration of 40mg/ml, while the to-be-marketed drug product dose is 4mg with a concentration of 16 mg/ml.

8.3. Review of the Safety Database

8.3.1. Overall Exposure

Studies API-N002-CL-A3 and API-N002-CL-A4 consisted of 60 total subjects 18-45 years of age (32 and 28 subjects, respectively). The safety data discussed below are from both trials and provide additional support to the Agency's previous findings of safety for the reference drug Narcan. All subjects were included in the safety group. The Applicant previously performed an analysis of published articles to support the safety of Naloxone Hydrochloride Nasal Spray at the time of the initial NDA submission and Dr. Nadel conducted a review of the literature at the time of her review in 2017. I conducted a review of the literature published since 2017 and did not find any safety signal.

Table 8 Summary of Safety Evaluations in Naloxone Hydrochloride Nasal Spray **Clinical Studies**

Items	**PK and Safety/Tolerability**	
Study Code	**N002-A3**	**N002-A4**
# Of Subjects (Treated)	32	28
Naloxone Dose, mg	4	10
Study Phase	I/III	
Type of Subjects	Healthy Adult Volunteers	
Dosing	Single Dose, IN vs IM and IV	
Major Safety Evaluations	General safety evaluations and nasal oropharyngeal tolerability assessment	General safety evaluations and olfactory evaluations by UPSIT
Study Design	Evaluator-blinded	Double-blinded
	Crossover	
Type of Controls	Naloxone HCl IM or IV	IN Placebo Control

Table 9 Safety Population, Size, and Denominators

Safety Database for the Study Drug[1] Individuals exposed to any treatment in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)					
Clinical Trial Groups	New Drug 4mg (n=27)	New Drug 10mg (n=27+28)	Active Control IM (n=28)	Active Control IV (n=30)	Placebo (n=28)
Healthy volunteers	27	555	28	30	28
Controlled trials conducted for this indication[2]	A3	A3 and A4	A3	A3	A4
All other trials conducted for this indication[3]	NA	NA	NA	NA	NA
Controlled trials conducted for other indications[4]	NA	NA	NA	NA	NA

[1] *Study drug* means the drug being considered for approval.
(b) (4)
[3] If placebo arm patients switch to study drug in open label extension, then the sample n should count those patients only once; do not count twice patients who go into extension from randomized study drug arm
[4] Include n in this row only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review.

8.3.2. Relevant characteristics of the safety population

Healthy women and men 18-45 years of age.

8.3.3. Adequacy of the safety database

60 subjects were included in study A3 and A4. Given that the Applicant is utilizing the 505(b)(2) pathway and

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relying on the Agency's previous findings of Narcan, this exposure is adequate for the purposes of this safety evaluation.

Demographics: The population studied was diverse with the following characteristics:

- The mean ages of subjects were 29.8±6.4 (ranged 18-43) years old; and 31.2±8.5 (Ranged 19-45) years old for Studies A3 and A4, respectively.
- The gender profile was about 37.5% male and 62.5% female for Study-A3, 42.9% and 57.1% in Study-A4.
- The racial and ethnicity profile showed that the majority of the subjects were African American (56.3%) in Study-A3 and Caucasians (82.1%) in Study-A4; 3.1% and 3.6% were Asian in study A3 and A4 respectively. 15.6% and 17.9% of subjects were Hispanics in Study-A3 and A4 respectively.
- Average weight of subjects was 74.2±13.8 kg in Study-A3, and 75.3±14.3 kg in Study- A4.

Table 10: Summary of Demographic Parameters (A3 and A4)

Study Code	A3	A4
# of Subjects	32	28
Age (Years)		
Mean ± SD	29.8±6.4	31.2±8.5
Range	18-43	19 - 45
Gender		
Male	12 (37.5%)	12 (42.9%)
Female	20 (62.5%)	16 (57.1%)
Race		
Caucasian	10 (31.3%)	23 (82.1%)
African American	18 (56.3%)	1 (3.6%)
Asian	1 (3.1%)	1 (3.6%)
Ethnicity		
Hispanic	15.6%	17.9%
Weight (kg)		
Mean ± SD	74.2 ± 13.8	75.3 ± 14.3

8.4. Adequacy of Applicant's Clinical Safety Assessments

8.4.1. Issues Regarding Data Integrity and Submission Quality

All data and documents in this application were electronically submitted following the guidance for electronic submission. The documents were organized in electronic Common Technical Document (eCTD) format. The overall quality of the submission was adequate. The organization and the ability to navigate the NDA were acceptable.

8.4.2. Categorization of Adverse Events

All adverse events (AEs) were coded by using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. The AEs were coded to a dictionary-derived term, a lowest level term (LLT), and a system organ class (SOC). The definitions and categorizations provided by the Applicant of treatment-emergent adverse events and serious adverse events are acceptable.

8.4.3. Routine Clinical Tests

The clinical laboratory assessments in Studies A3 and A4 consisted of hematology, comprehensive metabolic panel, urinalysis, at screening and final study visits. Drug and alcohol tests, pregnancy testing in females of childbearing potential and ECGs were performed at screening and at each study visits including the final visit in study A3 and A4. Blood sampling for pharmacokinetic analysis were collected for study A3.

8.5. Safety Results

8.5.1. Deaths, Serious adverse events, and severe adverse events

No deaths, no serious adverse events (SAE) and no severe adverse events were reported in studies A3 and A4.

8.5.2. Dropouts and/or Discontinuations Due to Adverse Effects

In study A3, 7 dropouts (out of 32 subjects) were reported, 3 drop-outs after 1 treatment period, 2 after 2 treatment periods, and 2 after 3 treatment periods. Study A3 dropout information is summarized in the table below. No dropouts were reported in study A4.

Table 11 Dropout Information in study A3

#	Reason for dropout/Early Termination (ET)	Treatment(s) Sequence *	Comment/TEAE
1	Unable to collect blood samples	C4-V1-V2-C3	dry throat
2	Withdrew consent due to schedule conflict	C3-C4-V1-V2	
3	No longer met inclusion #8: negative alcohol test	C4-V1-V2-C3	
4	Withdrew consent due to AE (leg inf)	C3-C4-V1-V2	leg infection
5	Study drug leakage	V1-V2-C3-C4	
6	Positive pregnancy test	V1-V2-C3-C4	Positive pregnancy test
7	**Met exclusion #8: abnormal ECG**	C4-V1-V2-C3	

* Visits marked in red represent missing study treatments. V1: Naloxone HCL nasal spray 4 mg dose (concentration 16mg/ml); V2: Naloxone HCL nasal spray 10 mg dose (concentration 40mg/ml), C3: Naloxone HCL 0.4 mg IM; C4: Naloxone HCL 2mg IV.

Reviewer comment: the Subject with an abnormal EKG in the above table is a 26-year-old African American woman with no prior medical history and on no concomitant medications who was terminated early from the study due to the development of a first-degree AV block on ECG, 9 days after receiving C4 (IV Naloxone). Her screening ECG ([(b) (6)]) displayed a PR interval of 193 msec (normal range 120-200 msec) and a PR interval of 180 msec on repeat ECG 6 minutes later. On the first treatment period pre-dose ([(b) (6)]) her PR was 189 msec. It was 185 msec 40 minutes after receiving C4, and 179 msec 6 hours post dose.
On [(b) (6)], her PR interval was found to be 201 (slightly above the upper limit of normal) and on repeat EKG 1 minute later, the PR segment was 206 msec. The subject was consequently terminated due to developing a first-degree AV block prior to receiving 2nd treatment sequence dose. No clinically relevant lab abnormalities were present. The significance of this ECG change is unclear. Note: The normal PR interval is between 120 and 200 msec. However, an Analysis of Electrocardiograms Obtained from 1000 Young Healthy Aviators[2] reported that some apparently healthy persons have longer PR intervals, with PR intervals as long as 280 msec having been reported in 1.6 percent of healthy aviators.

> *Note: In this NDA's initial clinical review, with the previous formulation [(b) (4)] Dr. Nadel notes that 2 subjects (out of 33 randomized) in the A2 study were terminated after the appearance of second-degree AV block. Both had high normal PR on their initial baseline ECGs, and both developed 1st and 2nd degree AV block. One of those subjects developed 1st degree AV block 45 minutes after receiving IM naloxone, which resolved, but on the subsequent visit was found to have a 2nd degree AV block and was terminated from the study drug. The second subject developed intermittent 1st degree AV block 40 minutes after receiving IN 4mg/mL followed by intermittent 2nd degree AV block 90 minutes after the dose and shortly after returned to NSR (normal sinus rhythm).*
> *"It is unclear what the significance of these ECG changes represents. Both subjects had high PR intervals at baseline, which may have contributed to them developing AV blocks irrespective of the naloxone administration. The subjects did remain asymptomatic, and their ECGs returned to NSR without any intervention or further degradation of their rhythms."*

8.5.3. Significant Adverse Events

No severe adverse events were reported in studies A3 and A4. Two moderate adverse events (Pregnancy and spider bite/leg infection) assessed as definitely not related to the treatment by the Applicant are discussed below.

8.5.4. Treatment Emergent Adverse Events and Adverse Reactions

In study API-N002-CL-A3, a total of 13 TEAES were reported; 2 TEAEs (Pregnancy and spider bite/leg infection) were assessed as moderate and definitely not related to the treatment. Both subjects were withdrawn from the study.
All other TEAE were mild: Dry throat and oral paresthesia were assessed as mild and causality unknown. All remaining mild TEAEs were either "likely unrelated" or "definitely unrelated".
The most common TEAE was headache with 4 occurrences, 1 reported in each treatment period, in 4 subjects. 1 of those subjects had migraine in addition to headache. Headache is listed as a possible adverse reaction in

the Narcan spray label.

Table 12: TEAE per treatment period in study A3 as assessed by the Applicant

Treatment	Lowest Level Term	Serious	Severity	Causality	Outcome of Adverse Event	Action Taken with Study Treatment
V1 (N002 4 mg IN)	Headache*	N	Mild	Unlikely related	Recovered/resolved	Dose not changed
	Leg infection	N	Moderate	Definitely not related	Recovered/resolved	**Drug withdrawn**
	Paresthesia oral	N	Mild	*Unknown*	Recovered/resolved	Dose not changed
V2 (N002 10 mg IN)	Dizziness	N	Mild	Unlikely related	Recovered/resolved	Dose not changed
	Headache	N	Mild	Unlikely related	Recovered/resolved	Dose not changed
	Lightheadedness*	N	Mild	Unlikely related	Recovered/resolved	Dose not changed
	Pregnancy	N	Moderate	Definitely not related	Not recovered/not resolved	**Drug withdrawn**
C3 (Naloxone Hcl 0.4 mg IM)	Headache	N	Mild	Definitely not related	Recovered/resolved	Dose not changed
C4 (Naloxone Hcl 2 mg IV)	Dry throat	N	Mild	*Unknown*	Unknown	Dose not changed
	Dysuria	N	Mild	Definitely not related	Recovered/resolved	Dose not changed
	Headache	N	Mild	Unlikely related	Recovered/resolved	Dose not changed
	Migraine*	N	Mild	Unlikely related	Recovered/resolved	Dose not changed
	Vomiting*	N	Mild	Unlikely related	Recovered/resolved	Dose not changed

* Those 4 TEAEs occurred in the same subject. N002: Naloxone Hydrochloride Nasal Spray

Reviewer comment: Headache is an adverse reaction listed on other naloxone products labels. In this PK study, headache occurred in one subject from each treatment arm. The causality is "likely related" rather than "unlikely related" per my assessment. I also recommend that headache to be added to the clinical trial safety / adverse reaction section of the label (highlights and section 6).

In study API-N002-CL-A4, the only TEAE observed was a "sprained ankle" that occurred after subject received placebo. It was assessed as moderate in severity and "definitely not related" to the study drug.

8.5.5. Laboratory Findings

In study A3, a CBC, a CMP, and a urinalysis were checked. I reviewed the lab results for each individual and found no clinically significant changes from the baseline screening labs. Two female subjects in study A3 had low hemoglobin at baseline (Hemoglobin (hgb) respectively 11.5 and 10.9) and had a further decrease in their hgb at EOS (10.6 and 9.5 respectively). One male subject had low hemoglobin at baseline (13.3) and a slightly lower hgb at EOS (12.9). He also had a slight decreased in his white blood cell count (wbc) from 4.42 to 3.44. Seven subjects had a mildly low or low normal wbc at screening (3.94, 4.07, 3.82, 4.20, 3.76 4.37, and 4.42 respectively) and a further mild decrease in wbc at EOS (3.26, 3.78, 3.34, 3.19, 2.94, 3.45, and 3.44

respectively). The second subject also had a slight decrease in their lymphocyte count 1.21 at screening to 1.14 at EOS and the fourth subject had a decrease in their neutrophil count at EOS 1.36 down from 1.41 at screening. The fifth subject also had a mild decrease in their neutrophil count (1.59 at EOS from 2.25 at screening) and lymphocyte count (1.09 at EOS from 1.26 at screening).
Note that 3 subjects had a mildly low wbc at screening that went up some at EOS.
One subject had a slightly elevated t.bili (1.4) at EOS and one subject had a slight direct bilirubin increase (D. bili 0.22) and was terminated due to pregnancy.
In study A4, a CBC, a CMP, and a urinalysis were checked. I reviewed the lab results for each individual and found no clinically significant changes from the baseline screening labs. One subject had a slightly low white blood cell count at EOS (3.7 down from 5.5 at screening) that was deemed not clinically significant. One subject had a slight elevation of his serum creatinine (1.1 to 1.36) at end of study deemed not clinically significant.

Reviewer comment: the mild decrease in hemoglobin in 3 subjects in the PK study (A3) can be attributable to the blood draws necessary for PK assessments. The changes in wbc counts, neutrophil counts and lymph count occurred mostly in subjects who had low cell counts at baseline. The significance of these changes is unclear.

8.5.6. Vital Signs and physical exams:

Study A3: One subject, a 28-year-old woman had low blood pressure 85/51 mm Hg 15 minutes after receiving IV Naloxone (C4) down from 103/68 and went up to 106/66 six hours later. Similar blood pressure measurement occurred 15 minutes after intranasal naloxone 10 mg in visit 4 with similar recovery. No intervention was necessary, and no symptoms were reported. This was assessed as not clinically significant. Please see paragraph 8.5.8 for a description of the nasal passages and oropharyngeal exam as part of the local safety evaluation for this study.
Study A4: One Subject developed bradycardia with a heart rate (HR) 42 bpm at the 10-min VS measurement after receiving Naloxone Hydrochloride Nasal Spray (baseline HR 60). His HR spontaneously went up to 61 bpm approximately 2 hours later. Otherwise, vital signs were within normal limits. General physical exam was reported as normal throughout the study. No symptom was reported, and no intervention reported either. This finding was assessed as not clinically significant.

8.5.7. Electrocardiograms (ECGs)

I reviewed study A3 and A4 subjects' ECGs and found no clinically significant changes from the screening ECG, except for one subject in study A3, who was terminated due to the development of a first-degree AV block on ECG 9 days after receiving C4 (Intravenous Naloxone). This was discussed further in section 8.4.2. I reviewed the QTcF intervals from the subjects' ECGs in study A3 and A4 and no QTc prolongation was observed in either study.

8.5.8. Local safety Evaluations results

Study A3

- NOME: The Applicant reported 105 minor incidents with score = 1, 115 incidents with score >1 and

that no difference in NOME score was observed between all study treatments.
I reviewed the NOME data for all the subjects in study A3. Of the 32 subjects enrolled in this study, 4 had normal NOME throughout the study; 21 subjects had very mild or mild findings (mostly very mild or mild nasal turbinate edema); one subject had nasal septal crusting and possible superficial excoriation that resolved on subsequent visits; 5 subjects were found to have moderate (level 3) right turbinate edema, and 1 subject was found to have severe (level 4) right turbinate edema on NOME assessments. Of these 6 subjects who had either moderate or severe NOME assessments, all but 1 already had moderate -severe right turbinate edema at the time they presented to their treatment visit (baseline of the visit), and 4 of those 6 subjects had those findings at baseline on visit 1, before any of the treatment was administered.
The subject with severe (grade 4) right turbinate edema had that finding at baseline on visit 1 (treatment V1, Naloxone Hydrochloride Nasal Spray 4 mg/0.25 ml) as well as throughout the rest of the study dosing visits. The rest of his NOME was reported as normal and the subject's self-assessment as well as the investigator's assessment were both reported as normal throughout the 4 visits. This subject completed all 4 treatments.
Of the 5 subjects who had moderate right turbinate edema, 3 dropped out reportedly for unrelated causes (unable to collect blood samples, scheduling conflict, positive pregnancy test), and completed all 4 treatments. In conclusion, I agree that no difference in NOME score was observed between all study treatments.

- IAF: No clinically significant abnormalities were reported in the study.
- SSA: 3 minor incidents with score = 1; and 6 incidents with score >1.
  I reviewed the data for subjects with moderate or severe self-reported nasal symptoms/incidents. Two subjects self-reported a total of 5 incidents of either moderate or severe nasal symptoms. One of them developed lightheadedness (moderate) after treatment V2 (Naloxone Hydrochloride nasal spray 10 mg/0.25ml) at visit 1 and developed moderate burning /pain as well as severe facial pain/pressure and severe headache/nausea (severe) after treatment C4 (Naloxone Hcl 2 mg IV) on visit 3. The second subject developed moderate headache after treatment C4 at visit 4. Both subjects completed all 4 treatment sequences. It is also notable that both these subjects had very mild or mild NOME findings, none had moderate nor severe findings.

Reviewer comment on local safety evaluation results: minimal nasal irritation/inflammation was found in most subjects (28/32) and the vast majority already had those findings at the visit 1 baseline before any drug was administered. Local irritation findings were spread across the 4 treatments. I agree that these are unlikely to be attributed to IN naloxone.

Study A4

Data was collected from 28 (12 male and 16 female) healthy adult volunteers, who were tested using the UPSIT. I reviewed the data for all the subjects in this study. The mean change in olfactory performance from baseline to 4 hours post-dose was -0.11 ± 0.42 in Treatment-P (placebo) versus -0.07 ± 0.38 in Treatment-T (naloxone 10mg IN). Five occurrences of decrease in UPSIT by ≥2 points with Naloxone Hydrochloride Nasal Spray (10 mg in 0.25 ml) and 7 occurrences with Placebo. Two subjects who had received placebo and one subject who had received Naloxone had a decrease in their olfactory performance from normosmia to mild

microsmia (olfactory performance score change from 5 to 4).

Reviewer comment: In conclusion, I agree that no significant change in olfactory functions was observed following administration of Naloxone Hydrochloride Nasal Spray at the dose strength of 10 mg (in 0.25 ml) and the concentration of 40 mg/ml when compared with placebo.

Reviewer comments on safety results from studies A3 and A4:
Overall, the safety data from the trials did not show any new safety signals. There were no deaths, serious adverse events (SAE) or severe adverse events. There were two moderate TEAEs in two subjects in the A3 trial which this reviewer agrees are unlikely related to the study drug. There were no clinically significant changes nor concerning changes observed in the vital signs, physical exam, laboratory data, or local safety assessments The PK data for Naloxone Hydrochloride (4 mg in 0.25 ml) Nasal Spray exceeded the comparator (0.4 mg IM injection). However, the exposure is within the exposures achieved with the initial approved dose range of the reference product (0.4 to 2 mg IV).

8.6. Study API-N002-CL-C

This is a retrospective observational study of patient encounters from electronic medical records of pediatric patients aged 0-3 who received medications administered intranasally (IN) at volumes of 0.25ml or more. Patients with a history of nasal injury, nasal obstruction, lesions to the nasal mucosa, history of nasal or sinus anomalies or dysfunction were excluded. The study endpoint was adverse drug events (ADE) related to IN dosing, and more particularly, any ADE defined as respiratory compromise (e.g., aspiration) resulting from IN drug delivery. The IN-administered medications were Midazolam, Fentanyl, Ketamine, Dexmedetomidine and/or additional sedative and analgesics.
A total of 571 cases (per-protocol population) was reported where volume of IN meds delivered ranged from 0.25 to 3.90 mL, and no ADE related to IN dosing volume were reported. 6 ADEs were reported, none was related to IN administration, per the Applicant's assessment.
We note that only 37 (6.6%) of 562 pts (571 cases) were of 1 year old or less.

Table 13: Summary of Reported ADE

Category	Post-Treatment Information		EP		PPP		AE Related to IN Dosing Volume
Primary Outcome Assessment	**Did Aspiration Occur During or after IN Dosing?**						
	Yes		0	(0%)	0	(0%)	0
	No		668	(100%)	**571**	(100%)	0
	Symptom Description	**MedDRA Code**					
Other Adverse Event(s)	Constipation	10010774	1	(0.1%)	1	(0.2%)	0
	Diarrhea	10012735	1	(0.1%)	1	(0.2%)	0
	Oxygen saturation decreased	10033318	1	(0.1%)	1	(0.2%)	0

	Rash	10037844	1	(0.1%)	1	(0.2%)	0
	Viral upper respiratory tract infection	10047482	2	(0.3%)	2	(0.4%)	0

We note one reported case of "oxygen saturation decreased" listed in the above table. The corresponding case report narrative provided was reviewed. The patient was a 20.53-month-old white male child who received 0.45 ml of Midazolam in each nostril (total IN dose of 0.9 mg) presumably pre-procedure. Per the provider's note, he "developed a brief episode of desaturation to 84 during the procedure but came back up immediately and remained with normal sats afterwards". This was not consistent with aspiration, and it was not considered to be related to IN delivery.

Table 14: IN Volume and ADEs Observed in PPP

IN Medication Administered	Indication for IN Intervention	# of Cases (percentage)	IN Delivery Volume (mL)		Number of Nostrils Dosed			Adverse Events	
			Average	Median (range)	1	2	3	Aspiration or IN-related	Others
Dexmedeto-midine	Transthoracic Echocardiography	53 (9.3%)	0.28	0.27 (0.25, 0.37)	53	0	0	0	0
Fentanyl	Analgesia	57 (10.0%)	0.42	0.42 (0.26, 0.74)	41	16	0	0	4
Ketamine	Sedation	4 (0.7%)	0.41	0.30 (0.30, 0.74)	3	1	0	0	0
Midazolam	Anxiolysis and Sedation	457 (80.0%)	1.00	1.00 (0.25, 3.90)	30	426	1	0	2
Total		**571**	**0.87**	**0.90 (0.25,3.90)**	**127**	**443**	**1**	**0**	**6**

The Applicant concludes that this retrospective study provides satisfactory safety data regarding the intranasal volume of 0.25 ml in young pediatric patients 0-3 years of age.

Reviewer comment:

We concur with the Applicant regarding their conclusion on the safety of the IN volume of 0.25ml in pediatric patients of all ages including neonates given the absence of serious respiratory complications related to intranasal administration of volumes 0.25 to 3.90 mL in this retrospective study. For the discussion regarding efficacy in the youngest pediatric populations, please refer to section 7.3.

Table 15: Demographic data from Study C.

Study Populations	Reported Population (RP)	Evaluable Population (EP)	Per Protocol Population (PPP)

# of Reported Cases			
Study Sites/Hospitals and Location			
Seattle Children's Hospital, Seattle, WA	400	400	400
Cincinnati Children's Hospital, Cincinnati, OH	53	53	53
Christus Trinity Mother Frances Hospital, Tyler TX	96	96	83
Loyola University Medical Center, Maywood, IL	119	119	35
Total # of IN Treatments (Reported Cases)	**668**	**668**	**571**
# of Subjects	**656**	**656**	**562**
Age at the time of IN Treatment			
Age (months), median (range)	23.0 (0.1 - 36.0)	23.0 (0.1 - 36.0)	23.4 (0.1 - 36.0)
Age Group, n(%)			
≤ 1 yr old	50(7.6%)	50(7.6%)	37(6.6%)
> 1 yr old ≤ 2 yr old	314(47.9%)	314(47.9%)	259(46.1%)
> 2 yr old ≤ 3 yr old	292(44.5%)	292(44.5%)	266(47.3%)
Weight (kg), mean ± SD	13 ± 2.5	13 ± 2.5	13 ± 2.3
Gender, n(%)			
Male	382(58.2%)	382(58.2%)	331(58.9%)
Female	274(41.8%)	274(41.8%)	231(41.1%)
Race, n(%)			
African American	25(3.8%)	25(3.8%)	22(3.9%)
American Indian/Native	3(0.5%)	3(0.5%)	3(0.5%)
Asian	50(7.6%)	50(7.6%)	48(8.5%)
Caucasian	378(57.6%)	378(57.6%)	334(59.4%)
Others	126(19.2%)	126(19.2%)	82(14.6%)
Unknown	74(11.3%)	74(11.3%)	73(13.0%)
Ethnicity, n(%)			
Hispanic or Latino	135(20.6%)	135(20.6%)	101(18.0%)
Non Hispanic or Latino	513(78.2%)	513(78.2%)	453(80.6%)
Unknown	8(1.2%)	8(1.2%)	8(1.4%)

8.7. Specific Safety Studies/Clinical Trials

A study of olfactory function (Study API-N002-CL-A4) was conducted to evaluate the effect on the olfactory function of subject receiving Naloxone Hydrochloride Nasal Spray intranasally. A retrospective observational pediatric study (Study API-N002-CL-C) was conducted to evaluate efficacy and safety of IN delivery of volume > 0.25 ml in young children. Please refer to sections 8.2.2 and 8.6, respectively, for a detailed review of these studies.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There were no carcinogenicity studies with naloxone hydrochloride submitted in this NDA. The applicant is relying upon the Agency previous finding of safety for Narcan (naloxone) injection, to support their application. Please see the pharmacology toxicology review by Dr. Carlic Huynh for details.

8.8.2. Human Reproduction and Pregnancy

There were no new reproductive and developmental toxicology studies with naloxone hydrochloride submitted in this NDA. The applicant is relying upon the Agency previous finding of safety for Narcan (naloxone) injection, to support their application. Please see the pharmacology toxicology review by Dr. Carlic Huynh for details. One pregnancy was reported in the PK study (study A3) and was assessed as non-related to the study drug. No further information was available on this.

8.8.3. Pediatrics and Assessment of Effects on Growth

The Division of Pediatric and Maternal Health (DPMH) was consulted to evaluate the safety and efficacy of this product for the entire pediatric age range and has concluded that no safety concern was identified with this product and that the Applicant's submitted analyses are supportive of the pediatric safety of the 0.25 mL IN spray volume in the youngest patients. Please see the review conducted by Dr. Ndidi Nwokorie, MD for additional information.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No instances of overdose were reported in the comparative bioavailability study (A3) or the olfactory function study (A4). The currently approved Narcan product labeling states there is no clinical experience with naloxone overdose in humans. Naloxone does not produce subjective effects or physical dependence and hence it does not have any known abuse potential. There is no data available regarding withdrawal and rebound.

8.9. Safety in the Post-market Setting

8.9.1. Safety Concerns Identified Through Post-Market Experience

Naloxone has been available since 1971. Substantial clinical evidence in published literature supports its continued use. In April 2015 at the time of the initial submission of this NDA, the Applicant submitted articles in the setting of a literature review regarding the safety of naloxone in the post-market setting since its original approval as Narcan® in 1971. The Applicant did not provide a summary of the articles at the time of the original submission. The Applicant has not submitted a post-marketing safety analysis with the re-submission either. Dr. Nadel who was the clinical reviewer for the initial submission reviewed the articles submitted then and did not find evidence of any new safety signals that would require any changes to the current naloxone label.
I conducted a review of the literature published since 2015 and a review of annual reports, specifically, the most recent PADER for Kloxxado® (NDA 212045, reporting period July 1, 2022 – Sept. 30, 2022), and the

following reports for Narcan nasal spray (NDA 208411): the most recent PADER (period Nov. 18, 2018 - Nov. 17, 2019), PBRER (period Oct. 3, 2021, to Oct. 2, 2022) and New/Annual report with PMR/PMC status (reporting period Nov. 18, 2021 - Nov. 17, 2022).
The Narcan® nasal spray PBRER reports a total of 6 cases of Naloxone-associated pulmonary edema following recreational opioid overdose found in the literature[4], causality with Naloxone was assessed as possible. Pulmonary edema following Naloxone use is rare and has been reported more often in the post-operative setting than with recreational opioid overdose. Otherwise, no new safety concern was found from the above review.
In conclusion, the review of the available data from spontaneous reporting and from literature did not identify any new safety concerns reported in post-marketing, other than the adverse events listed in the label.

8.9.2. Expectations on Safety in the Post-market Setting

Substantial clinical evidence in the published literature demonstrates the overall favorable safety profile of Naloxone. No post-marketing requirements are recommended at this time.

8.9.3. Additional Safety Issues From Other Disciplines

8.10. Integrated Assessment of Safety

Naloxone is a life-saving medication that reverses opioid induced respiratory depression. The main risk of naloxone when used for the reversal of opioid overdose is severe opioid withdrawal in the opioid dependent patient. This risk is described in the label for all naloxone products, as well as the importance of seeking emergency medical care and of medical monitoring after the use of Naloxone. A review of the literature and of available safety data from other Naloxone products did not reveal any new signal.
A review of the clinical studies submitted by Amphastar, the PK study and the olfactory function study, revealed no new safety signal with the use of IN naloxone 4 mg at a 16mg/ml concentration. The most common TEAE was headache, (4 occurrences), one reported in each treatment period, in 4 subjects. Headache is listed as a possible adverse reaction in other naloxone products (Narcan® spray and Kloxxado®) PRLP. Dizziness, lightheadedness, paresthesia oral, dry throat, dysuria, leg infection, pregnancy, migraine, and vomiting were reported as well. All adverse events were mild to moderate in severity. No deaths, serious adverse events, or severe adverse events were reported. Review of local toxicity evaluations (nasal cavity and oropharyngeal exams as well as olfactory nerve evaluations) did not raise any safety concern. The safety of this intranasal product, and specifically of its volume of administration in pediatric patients including the youngest patient populations, is supported by the data provided by the Applicant in the retrospective observational pediatric study described earlier.
In conclusion, the avilable data did not reveal any specific safety concerns related to the clinical use of Amphastar's Naloxone Hydrochloride Nasal Spray that precludes approval.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee (AC) meeting was not held to discuss this specific product.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The proposed prescribing information for Naloxone Hydrochloride Nasal Spray is based on the approved labeling for the listed drug Narcan® inj. (NDA 016636). The Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP) and the Division of Pediatric and Maternal Health (DPMH) were consulted regarding the proposed labeling. I completed the labeling review. I identified certain sections such as the highlights section and section 6 (adverse reactions), that needed revision. Additional revisions were also needed to make this product labeling consistent with most recently approved naloxone nasal spray products. These revisions were communicated to the Applicant along with modifications requested by CMC, DMEPA, clinical pharmacology, and pharmacology toxicology.
Labeling discussions were started with the Applicant following the team's recommendations and are ongoing at the time of this writing.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not recommended at this time.

12. Post marketing Requirements and Commitments

No post marketing requirements or commitments are recommended at this time.

13. Appendices

13.1. References

- **Ref. 1**: https://www.federalregister.gov/documents/2022/11/16/2022-24874/safety-and-effectiveness-of-certain-naloxone-hydrochloride-drug-products-for-nonprescription-use).

- **Ref. 2**: PACKARD JM, GRAETTINGER JS, GRAYBIEL A. Analysis of the electrocardiograms obtained from 1000 young healthy aviators; ten year follow-up. Circulation. 1954 Sep;10(3):384-400. doi: 10.1161/01.cir.10.3.384. PMID: 13190611.
- **Ref. 3**: (Hosseini et al. In Vitro Measurement of Regional Nasal Drug Delivery with Flonase,® Flonase® Sensimist,™ and MAD Nasal™ in Anatomically Correct Nasal Airway Replicas of Pediatric and Adult Human Subjects. J Aerosol Med Pulm Drug Deliv. 2019 Dec;32(6):374-385. doi: 10.1089/jamp.2019.1523. Epub 2019 Aug 29. PMID: 31464547.)
- **Ref. 4**: Kummer RL, Kempainen RR, Olives TD, Leatherman JW, Prekker ME. Naloxone-associated pulmonary edema following recreational opioid overdose: A case series. Am J Emerg Med. 2022;53:41-3 and Bashline C, Bernstein H, Case N, Connelly W, Salvatore JD, Lee G et al. Consequences of Non-EMS Treatment of Opioid Overdose in the Out-of-Hospital Setting. J Emerg Med Serv. 2022

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): API-N002-CL-A3

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 9 (including sub-Investigators)		
Number of investigators who are Applicant employees (including both full-time and part-time employees): None identified		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None identified		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator," and stated a total of 1 investigator and 8 sub investigators were listed and study API-N002-CL-A3 was performed through the contract research organization, WCCT Global, LLC in California. The form certified that they had no financial interests or arrangements to disclose.

Covered Clinical Study (Name and/or Number): API-N002-CL-A4

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13 (including sub-investigators)		
Number of investigators who are Applicant employees (including both full-time and part-time employees): None identified		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None identified		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator," and stated a total of 1 investigator and 12 sub investigators were listed and study API-N002-CL-A4 was performed through the contract research organization, Northeast Medical Research Associates, Inc. in Massachusetts. The form certified that they had no financial interests or arrangements to disclose.

13.3. Attachments

Attachment 1: Modeling of Nasal Spray Run-Off Volumes in Neonate and Pediatric Nasal Airways (≤ 3 Years of Age) by Physiology-Based, Computational Fluid Dynamics (CFD) Simulations – Executaive summary – For more details see full report submitted by Applicant on January 6, 2023.

Attachment 2: Additional simulation study using Hosseini's study parameters submitted by Applicant on February 1, 2023.

Attachment 3: Sensitivity analyses across different air flow rates submitted by Applicant on February 13, 2023.

23 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CORINNE A AHMAR
03/07/2023 10:05:00 AM

SILVANA BORGES
03/07/2023 10:57:37 AM
I concur with Dr. Ahmar's recommendation to approve this application.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208969
Priority or Standard	Standard
Submit Date(s)	April 20, 2016
Received Date(s)	April 20, 2016
PDUFA Goal Date	February 19, 2017
Division / Office	DAAAP/ODE II
Reviewer Name(s)	Jennifer Nadel, MD
Established Name	Naloxone HCl Nasal Spray
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Opioid Antagonist
Applicant	Amphastar Pharmaceuticals, Inc.
Formulation(s)	Intranasal Spray
Dosing Regimen	(b) (4)
Indication(s)	Opioid Overdose
Intended Population(s)	Out-of-Hospital Treatment of Opioid Overdose

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Complete response is recommended for the reasons described below.

1.2 Risk Benefit Assessment

This application is to support the product, (b) (4) utilizing the 505(b)(2) pathway with the reference drug Narcan (NDA 016636). It is meant for out-of-hospital treatment of opioid overdose for use in pediatric and adult patients of all ages. Each administration of the product is designed to give (b) (4) of naloxone via the intranasal route.

The Applicant's required clinical program consisted of demonstrating comparable (or higher) pharmacokinetics of (b) (4) vs. an approved route of administration of naloxone, in healthy volunteers. This was the agreed upon clinical program, given that it would be unethical to administer a novel naloxone drug-device product in an emergency, immediately life-threatening situation in the context of a clinical study when there are already approved and effective alternatives available. The Applicant submitted the results of two comparative bioavailability trials (b) (4)

Although the product met the pharmacokinetic standard, further review of this product raised additional concerns. James Schlick from the Division of Medication Error Prevention and Analysis (DMEPA) reported that the Applicant had determined during formative testing that, " (b) (4)

(b) (4)

(b) (4)

(b) (4)

The Human Factors validation study demonstrated five failures to use the product correctly. (b) (4)

Given the DEMPA findings, I do not think that the benefit this product may provide can outweigh the significant risk of failure to deliver a dose that has been established to be effective.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

Naloxone is an opioid antagonist.

The Applicant developed (b) (4) as a combination drug-device product and is submitting it under Section 505(b)(2) of the Food, Drug, and Cosmetics Act (FD&C Act). (b) (4) is a single-use intranasal (IN) spray that delivers (b) (4) of naloxone hydrochloride (HCl) via (b) (4) (b) (4) is intended for out-of-hospital use to reverse opioid overdose. (b) (4) is designed for a caregiver or untrained layperson to administer naloxone in the event of an opioid overdose.

2.2 Tables of Currently Available Treatments for Proposed Indications

Naloxone (Narcan) was initially approved in 1971. Naloxone is approved to treat opioid overdose. Narcan is no longer marketed; however, multiple generics are currently available. These products are generally intended for use in a healthcare setting. Narcan Nasal Spray and Evzio are specifically approved for use in the community. Off-label kits with naloxone also are being used in the community. There are three Naloxone products approved under and NDA including the original Narcan, though it has been discontinued (not for reasons of safety or effectiveness) and only its generics are available.

Table 1: Current Naloxone Treatment Options

Drug Product Name	NDA	Approval Date	Dose Form
Narcan	016636	4/13/1971	Injection
EVZIO (Naloxone HCl)	205787	4/3/2014	Injection
Narcan Nasal Spray	208411	11/18/2015	Nasal Spray

2.3 Availability of Proposed Active Ingredient in the United States

There are approved drug products containing the active ingredient naloxone in the United States (Table 1); Evzio and Narcan nasal spray are approved with the same indication as (b) (4) Naloxone is included as an active ingredient in several products in combination with opioid ingredients for the treatment of opioid dependence and pain. It is generally included in these products to deter abuse of the opioid component.

2.4 Important Safety Issues With Consideration to Related Drugs

There are several warnings on the label for naloxone regarding acute opioid withdrawal. Naloxone may cause an abrupt precipitation of opioid withdrawal. Some of the common symptoms of opioid withdrawal include agitation, anxiety, muscle aches, rhinorrhea, diaphoresis, diarrhea, vomiting, and pruritus. In neonates withdrawal may be life-threatening. Abrupt postoperative reversal of opioids has been shown to lead to

adverse cardiovascular events such as hypotension, hypertension, ventricular tachycardia, ventricular fibrillation, and pulmonary edema.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2: Key Presubmission Regulatory Activity

Date	Meeting/Submission Type	Key Comments
2/10/2015	Pre-IND Meeting (PIND 124672)	• 505(b)(2) pathway appropriate • PK standards established by the Division in lieu of efficacy studies given ethical concerns associated with evaluating the efficacy of a novel naloxone product • (b) (4)
3/27/2015	Fast Track designation granted	
10/13/2015	Pediatric Study Plan agreement	
11/5/2015	Type B Pre-NDA Meeting	• FDA expressed concern that (b) (4) for pediatrics • HF validation study showed failures that may impact efficacy of product • Co-packing two dosing units is planned
1/12/2016	Rolling Review granted	

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. The documents were organized in electronic Common Technical Document (eCTD) 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 14 investigators were listed and the studies were performed through the contract research organization, (b) (4)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The final CMC review is pending at this time. There were no significant chemistry, manufacturing and controls findings that would impact the safety or efficacy evaluation.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The final pharmacology/toxicology review is pending at this time. There were no significant pharmacology toxicology findings that would impact that safety or efficacy evaluation.

4.4 Clinical Pharmacology

The clinical pharmacology review was conducted by Srikanth Nallani, PhD, with secondary concurrence by Yun Xu, PhD. According to the clinical pharmacology team, this NDA is acceptable. The PK findings showed that (b) (4) was able to exceed the plasma concentration of the reference product, and it accomplished this in the early critical period. This is seen in Figure 1. The Applicant tested (b) (4)

Figure 1 PK of (b) (4) (Naloxone IN (b) (4) vs. Naloxone IM 0.4 mg

Taken from page 8 of the Summary of Clinical Pharmacology Studies

4.4.1 Mechanism of Action

Naloxone is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites.

4.4.2 Pharmacodynamics

When naloxone hydrochloride is administered intravenously, the onset of action is generally apparent within two minutes. The time to onset of action is shorter for intravenous compared to subcutaneous or intramuscular routes of administration. The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride[1].

4.4.3 Pharmacokinetics

See section 4.4

[1] From the label for Narcan NDA 016636 (the reference product).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3: Clinical and Human Factors Studies Submitted in Support of this Application

Clinical Trial	Population	Number of Subjects	Relevance
(b) (4)			

Comparative bioavailability data between the proposed product and the reference product were the only required clinical data to support this application.

(b) (4) coordinated human factors testing of the device. (b) (4) The Applicant submitted this additional data from human factors testing to support use of the product.

5.2 Review Strategy

The data from the API-N002-CL-(b) (4) study contain the actual to-be-marketed formulation at the planned dose of one spray (b) (4) in one nostril, and this is what will be focused on in this review. The Applicant refers to this formulation as N002 and so that is how it will be referred to in this review. I reviewed the PK studies submitted for systemic safety and local safety (results from the nasal and oropharyngeal exams). The Applicant is referencing the approved product Narcan, (b) (4) Given that that the new product will be dosed via the nose, I am paying particular attention to the nasal exam and nasal symptoms.

5.3 Discussion of Individual Studies/Clinical Trials

(b) (4)

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- Investigator Assessment Findings (IAF)[20]

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. 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, 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 clinical pharmacology review of the comparative bioavailability trials, API-N002-CL-(b) (4) and API-N002-CL-(b) (4) naloxone delivered by the IN device and the standard IM delivery, N002 met the pharmacokinetic requirements set forth by the Division.

While the PK studies showed that N002 met the criteria to rely on the Agency's previous findings of effectiveness of Narcan, the review identified several deficiencies with the product. The Division had previously discussed in meetings with the Applicant our concern (b) (4) While the PK results in the Pivotal studies were successful, in pediatrics (b) (4). This may lead to decreased efficacy and unreliability in the pediatric population.

Another deficiency of this drug-device product is related to problems with (b) (4) On DMEPA's evaluation of the product, they found (b) (4) Because of this, I cannot be certain that PK data from this scenario would meet our standard for approval. (b) (4) is concerning and in my opinion makes this product unreliable.

(b) (4)

(b) (4)

(b) (4)

6.1 Indication

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

(b) (4)

6.1.1 Methods

See section 5.3.

6.1.2 Demographics

See section 7.2.1.

6.1.3 Subject Disposition

See section 7.3.3.

6.1.4 Analysis of Primary Endpoint(s)

Not applicable.

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Additionally, the Applicant also submitted a study titled "(b) (4) Although this study may provide supportive safety and efficacy information, it was not considered further because it does not involve the product discussed in this NDA. (b) (4) .

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 Naloxone HCl Nasal Spray 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 to demonstrate that the PK parameters (i.e., AUC and Cmax) meet or exceed the comparator product values. (b) (4)

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

(b) (4) The safety data discussed below are from both trials and provide additional support to the Agency's previous findings of safety for the reference drug Narcan. All of the subjects were included in the safety group. The Applicant also performed an analysis of the literature to support the safety of (b) (4)

7.1.2 Categorization of Adverse Events

All AEs were coded by using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.1. The AEs were coded to a preferred term (PT) and a system organ class (SOC). All subjects were coded using the same MedDRA dictionary. The Applicant's categorization of adverse events is acceptable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

(b) (4) The data across both of these studies was pooled to estimate incidence of adverse events.

7.2 Adequacy of Safety Assessments

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

Exposure
Sixty-nine subjects were included in the PK studies. Because the Applicant is utilizing the 505(b)(2) pathway and relying on the Agency's previous findings of Narcan, this exposure is adequate for the purposes of this safety evaluation.

Demographics
(b) (4)

Table 6: Summary of Demographic Parameters ((b) (4) and (b) (4)

(b) (4)

Taken from page 15 of the Summary of Clinical Safety

7.2.2 Explorations for Dose Response

The submission did not include a formal analysis to evaluate a dose response with regards to safety. (b) (4)

7.2.3 Special Animal and/or In Vitro Testing

No data was submitted to inform a discussion for this section.

7.2.4 Routine Clinical Testing

The safety monitoring plan is outlined for the pivotal trials in section 5.3, which appear adequate for this population. There were no new safety signals that arose during the studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

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.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in these trials.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAE).

7.3.3 Dropouts and/or Discontinuations

(b) (4)

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8 Postmarket Experience

Naloxone has been available since 1971. There is substantial clinical evidence of published literature to support its continued use. A summary of the literature provided by the Applicant is located in Section 9.1.

9 Appendices

9.1 Literature Review/References

The Applicant conducted a literature review to look for any updates in the known safety and/or efficacy of naloxone since its original approval as Narcan in 1971. 37 articles were submitted and they were published between 1976 and 2016. The topics included safety and effectiveness of naloxone via different routes of administration, naloxone administration in situations that occur outside of the hospital, intranasal use, pharmacokinetics of naloxone, and neonatal effects. The Applicant did not give reasoning for why these particular articles were chosen and did not provide a summary of the articles. I reviewed the articles submitted and did not find evidence of new safety signals which would require any changes to the current naloxone label.

9.2 Labeling Recommendations

I have recommended a complete response for this product. If the Applicant resubmits this application, I would recommend they make changes to the proposed label. In the current label (b) (4) The Division would recommend that the Applicant modify the label in that area as well.

9.3 Advisory Committee Meeting

An Advisory Committee (AC) meeting was not held to discuss this specific product. However, a general matters joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held to discuss naloxone products for community use.

Several questions for voting and discussion were presented to the committee. In general the committee was asked to discuss what the best dose of naloxone is and if our standard for approval, which has been demonstration of the PK of a new product meets or exceeds that of 0.4 mg IM naloxone injection, is still sufficient.

The committee was not able to come to a consensus on the issue regarding whether the standard of 0.4 mg is too low. Some members felt there was a need for a higher standard to ensure more overdose victims could be reversed. Others argued the risks of precipitating withdrawal and also the lack of evidence that 0.4 mg is not high enough.

When this question was voted on, the vote was essentially split with 13 members wanted to keep the current standard and 15 members voting to increase the standard.

The committee also voted 21 to 7 on whether to have the same standard in adults and pediatrics, with more members favoring having the same standard. Concern was expressed that the 0.4 mg standard is too low for pediatrics.

Although there was limited time available to discuss how to differentiate multiple doses in labeling, when available, some committee members noted a high potential for confusion among laypersons and favored not having multiple strengths available. Others noted that if the right dose is established that will work in the vast majority of adults and children, multiple doses are not necessary and it is an unnecessary exercise to try and describe different doses in labeling.

9.4 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: 208969

Submission Date(s): April 19, 2016

Applicant: Amphastar Pharmaceuticals, Inc.

Product: (b) (4)

Reviewer: Jennifer Nadel, MD

Covered Clinical Study (Name and/or Number): Protocol API-N002-CL-(b) (4)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: (b) (4)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None identified		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None identified		
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)): Compensation to the investigator for conducting the study where the value		

could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator," and stated a total of (b) (4) *investigators were listed and the study was performed through the contract research organization,* (b) (4) *The form certified that they had no financial interests or arrangements to disclose.*

Clinical Investigator Financial Disclosure
Review Template

Application Number: 208969

Submission Date(s): April 19, 2016

Applicant: Amphastar Pharmaceuticals, Inc.

Product: (b) (4)

Reviewer: Jennifer Nadel, MD

Covered Clinical Study (Name and/or Number): Protocol API-N002-CL- (b) (4)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: (b) (4)		

Number of investigators who are sponsor employees (including both full-time and part-time employees): None identified		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None identified		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator," and stated a total of (b) (4) investigators were listed and the study was performed through the contract research organization, (b) (4) The form certified that they had no financial interests or arrangements to disclose.

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

/s/

JENNIFER L NADEL
01/10/2017

JOSHUA M LLOYD
01/11/2017