CLINICAL REVIEW

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(Proposed) Trade Name	
Applicant	Hikma Pharmaceuticals USA Inc
Dosage Form(s)	Nasal Spray
Applicant Proposed Dosing Regimen(s)	8 mg single-dose
Applicant Proposed Indication(s)/Population(s)	Emergency treatment of known or suspected opioid overdose
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	

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1. Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
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
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
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
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
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
PP	per protocol
PPI	patient package insert
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
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

2. Executive Summary

2.1. Product Introduction

Naloxone is a nonselective opioid receptor antagonist, with the greatest affinity for the mu receptor. Naloxone antagonizes opioid effects by competing for the mu, kappa, and sigma opiate receptor sites in the Central Nervous System (CNS).

Naloxone nasal spray is a single-use, drug-device combination product intended for use in the community. The Applicant proposes to market Naloxone nasal spray using the commercially available device from the device manufacturer (b) (4) in one strength (8 mg) that delivers 100 µl in a single intranasal spray and is for use in patients of all ages, both adults and children. The Applicant plans to rely on the previous findings of efficacy and safety for the reference product, Narcan (NDA 016636), which is approved for known or suspected opioid overdose. Two pharmacokinetic (PK) studies were submitted to provide a scientific bridge between the proposed product and the reference product.

2.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has supported efficacy of 8 mg Naloxone by demonstrating comparable (or higher) pharmacokinetics in healthy volunteers in relation to an approved route of administration of naloxone.
The 8 mg Narcan with 20% alcohol demonstrated higher systemic exposure to naloxone in comparison to the reference drug 0.4 mg IM dose, 14-fold greater Cmax, and 10-fold greater AUCs. The Cmax of the 8 mg Narcan with 20% alcohol did not exceed that of the 2 mg IV injection, but the corresponding AUClast and AUC0-inf values were 42 and 48% greater than a single 2 mg IV injection. In addition to referencing the safety of Narcan, the Applicant supported the safety of the product with a literature review indicating a wide safety margin for use of naloxone for the treatment of respiratory depression secondary to opioid overdose.

2.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Naloxone is a nonselective opioid receptor antagonist with the greatest affinity for the mu-opioid receptor developed to reverse life-threatening opioid overdose and prevent hypoxia associated with injury and death. The reviewer tentatively recommends a complete response on the basis of deficiencies in other disciplines. Refer to the respective discipline reviews for details.

Opioid overdose is a major problem in the United States. It contributes to a significant number of accidental deaths. Centers for Disease Control and Prevention (CDC) data indicated that in 2017 opioids were involved in 47,600 overdose deaths (67.8% of all drug overdose deaths). Overdose can occur in household contacts of a patient prescribed opioids by accidental exposure or through intentional misuse and abuse. Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that may lead to significant morbidity and mortality due to irreversible hypoxic injury. Death due to overdose from most opioids may be preventable with the immediate administration of an opioid antagonist such as naloxone.

It is known to be an effective treatment for suspected opioid overdose if an adequate dose is administered in time. There are currently two FDA approved naloxone products for use in adults and pediatric patients in the community: Evzio (naloxone hydrochloride injection; NDA 205787) was approved on April 3, 2014, and is a prefilled auto-injector for intramuscular and subcutaneous use that delivers a single 0.4 mg dose of naloxone hydrochloride per injection, and Narcan (naloxone hydrochloride; NDA 208411) Nasal spray was approved on November 18, 2015, and consists of a single-dose device of 4 mg dose of naloxone in 0.1 ml.

As more potent and faster onset synthetic opioids are being implicated in a growing proportion of opioid overdose deaths, larger doses of antagonist may be necessary than are available in currently approved single-dose devices to reverse the opioid overdose. Information on reports from emergency medical services on multiple naloxone administration (MNA) suggested that the percentage of patients receiving MNA increased from 14.5% in 2012 to 18.2% in 2015, which represents a 26% increase in MNA in 4 years. Some research has shown that the clinical response time with currently available Naloxone products was slower and more administrations were required to achieve the desired effect. This information raises the question regarding the overall effectiveness of current naloxone dosages given the rise in synthetic opioid overdose.

The efficacy of the Naloxone product is supported by a scientific bridge between the proposed product and the reference product through two pharmacokinetic (PK) studies. The Applicant submitted pharmacokinetic data that demonstrated that the

pharmacokinetic profile of 8 mg Naloxone nasal spray containing 20% delivered naloxone at greater than the lowest approved dose of the reference product, particularly in the early critical time period after drug administration. There are no clinical efficacy data for this product, no comparative efficacy data between this product and other approved naloxone products, and the application contains no evidence that this product will result in improved outcomes in reversing synthetic opioids.
The Cmax value was lower than the Cmax for the highest labeled dose in the reference product but the AUC exceeded the highest labeled dose of the reference product. Doses far exceeding those in the reference product are reported to have been well-tolerated in the literature and provide additional support for the safety of the product. The main risks of naloxone are severe precipitated opioid withdrawal and associated cardiovascular risks. Cardiac arrhythmias, cardiac arrest and death have been reported in postoperative reversal of opioid depression and have primarily occurred in patients with pre-existing cardiovascular disorders. No major safety issues related to 8 mg Naloxone nasal spray with 20% alcohol were identified in the review. Common adverse events from both randomized studies were dizziness, headache, presyncope, abdominal pain, asthenia, and nasal discomfort. The safety profile is acceptable. The FDA Adverse Event Reporting System can adequately monitor for any long-term effects that may occur in a community setting.
As with other approved naloxone products, the risk of acute opioid withdrawal is outweighed by the benefit of reversing a life-threatening overdose. Approval of 8 mg Naloxone nasal spray containing 20% of alcohol in the treatment of known or suspected opioid overdose in the adult and pediatric population is supported by the available evidence of efficacy and safety from a clinical perspective.

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 (CNS) depression that may lead to irreversible hypoxic injury Opioid overdose contributes to a significant number of deaths that can occur in a variety of settings The majority of fatalities arise in non-medical facilities	Opioid overdose is a serious life-threatening condition that contributes to a significant number of deaths.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Rates of increase in opioid overdose cases are highest for high potency opioids such as fentanyl and carfentanyl The percentage of patients receiving multiple naloxone administrations (MNA) increased from 14.5% in 2012 to 18.2 in 2015, which represents a 26% increase in MNA in 4 years	Patients can experience symptoms that are severe, contributing to the high morbidity and mortality rates. The recent rise in synthetic opioid represents an unmet medical need
Current Treatment Options	There are multiple drugs currently approved by FDA for the treatment for suspected opioid overdose The duration of antagonists such as Naloxone are generally shorter than the duration of action of most opioids Multiple naloxone administration of Naloxone is sometimes required with high potency opioids and reports of the need for multiple naloxone administrations are increasing over time	There are FDA-approved treatments options for patients with opioid overdose, however high potency opioids may require a higher dose and longer duration of action of naloxone Wide availability of potent opioids in the community may require administration of multiple doses of naloxone The treatment armamentarium would benefit from a Naloxone formulation that delivers a fixed efficacious optimal initial dose intended to be used in all settings by anyone including non-medically trained individuals

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The efficacy of the Naloxone product is supported by a scientific bridge between the proposed product and the reference product through two pharmacokinetic (PK) studies. The Applicant submitted pharmacokinetic data that demonstrated that the pharmacokinetic profile of 8 mg Naloxone nasal spray containing 20% delivered naloxone at greater than the lowest approved dose of the reference product, particularly in the early critical time period after drug administration. There are no clinical efficacy data for this product, no comparative efficacy data between this product and other approved naloxone products, and the application contains no evidence that this product will result in improved outcomes in reversing synthetic opioids.	The available data provide substantial evidence to support the effectiveness of Naloxone for adult and pediatric population
Risk and Risk Management	The most frequent adverse events with 8 mg Naloxone containing 20% of alcohol from two PK trials were dizziness, headache, abdominal pain, presyncope, nasal discomfort. All adverse events were mild to moderate in severity. Nasal and olfactory tests results do not raise any significant safety concerns. There were no deaths, serious adverse events, study discontinuations/dropouts due to adverse events Delay or inadequate exposure of Naloxone are life-threatening and may lead to permanent disabilities Recurrent respiratory and central nervous system depression with duration of action of opioid may exceed duration of action of naloxone Naloxone could potentially cause withdrawal symptoms in opioid dependent individuals, however, these symptoms are generally not life-threatening There are no comparative efficacy or safety data between this product and other naloxone products to inform prescribing decisions when choosing a product for opioid reversal	There are no safety concerns with use of 8 mg Naloxone containing 20% of alcohol There are no data to suggest that this product would result in delayed or inadequate exposure compared to other approved naloxone products There is no need for risk mitigation beyond the information provided in the labeling The FDA Adverse Event Reporting System can adequately monitor for any pong-term adverse events that may occur with off-label use of Naloxone

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		It is possible to precipitate an acute withdrawal syndrome in opioid tolerant patients, however, these symptoms are generally not life-threatening Current practice clinical guidance needs to be followed for choice of Naloxone product for known or suspected opioid overdose

2.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	□	61`		[e.g., Sec 6.1 Study endpoints]
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.			

3. Therapeutic Context

3.1. Analysis of Condition

Opioid overdose is a major public health problem in the United States and other countries. In the US, opioid overdose contributes to a significant number of accidental deaths. Center for Disease Control and Prevention (CDC) data indicated that in 2017 drug overdose deaths were more than 70,000 and almost 68% involved a prescription or illicit opioid. The sharpest increase occurred among deaths related to fentanyl and fentanyl analogs with more than 28,000 overdose deaths.

Accidental or intentional overdose and death associated with the use, misuse, and abuse of illicit and prescription opioids is a public health crisis in the United States. Opioid overdose can occur in a patient prescribed an opioid medication or in household contacts of the patient, or in people who misuse and abuse opioids. Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that may lead to significant morbidity and mortality due to irreversible hypoxic injury.

3.2. Analysis of Current Treatment Options

Multiple drug products containing the active ingredient naloxone are available and marketed in the United Sates. Naloxone is an effective treatment for suspected opioid overdose if an adequate dose is administered in time. Currently there is no convincing evidence that the currently available treatment options are insufficient in successfully reversing opioid overdoses in the community. However, as more potent and faster onset opioids have been implicated in a growing proportion of opioid overdose deaths, multiple administrations of naloxone to achieve reversal of an opioid and higher dose/target plasma level of Naloxone may be needed than are available to reverse opioid overdose before hypoxia results in irreversible injury. It is possible that in the presence of physical dependence on opioids, naloxone will produce opioid withdrawal symptoms, which may appear within minutes of administration and subside in about 2 hours. The severity and duration of the withdrawal syndrome is related to the dose of naloxone and to the degree and type of opioid dependence.

Narcan (Naloxone hydrochloride; NDA 16636) was approved in April 1971, and is available for subcutaneous, intramuscular, and intravenous use for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids. Narcan is also indicated for diagnosis of suspected or known acute opioid overdosage. When naloxone hydrochloride is administered by intravenous injection (IV), the onset of action is generally apparent within 2 minutes; the onset of action is slightly less rapid when it is administered by subcutaneous injection (SC) or intramuscular injection (IM).

Injectable formulations of naloxone have been FDA approved for the treatment of opioid overdose since 1971. The product labels recommend initial doses of 0.4mg to 2mg naloxone by the IM or IV route of administration, followed by repeat doses up to a total dose of 10mg. Nalmefene (Revex) injectable was approved by FDA in 1995 (NDA 020459). It was indicated for complete or partial reversal of opioid drug effects and management of known or suspected opioid overdose and it was available as a sterile solution for IV, IM and SC administration. Nalmefene was supplied in two concentrations: 100 µg/ml dosage strength for postoperative opioid depression with initial dose 0.25 µg/kg followed by 0.25 µg/kg incremental doses at 2-5 minutes intervals until desired degree of opioid reversal is obtained and 1 mg/ml dosage strength with initial dose for non-opioid dependent patients is 0.5 mg/70 kg, may be followed with second dose of 1 mg/70 kg 2-5 minutes later. Nalmefene was discontinued in 2014 not for safety or efficacy reasons. Generic versions of Nelmefene are currently available in the community.

Two naloxone products, Evzio (naloxone hydrochloride injection, NDA 205787) Auto-injector for intramuscular or subcutaneous use and Narcan (naloxone hydrochloride, NDA 208411) nasal spray have been approved in 2014 and 2015 respectively and are currently available in the US. These products represent an effort to develop and market products that can be administered by non-medically trained individuals and are intended for community use.

Each injection of Evzio delivers 0.4mg of naloxone HCL in pre-filled autoinjector intramuscularly or subcutaneously intended for use in the community. Narcan nasal spray consists of a single-dose device of 4 mg dose of naloxone in 0.1 ml. Generic naloxone products for injection are currently available and are being used in improvised nasal naloxone devices in the community as a less costly alternative to the products approved for community use.

There is evidence, that the off-label use of naloxone by the intranasal route has been effective in reversing opioid overdose in many cases. However, the lowest effective dose of naloxone is unclear, leaving the question as to whether there are patients that could have benefited from a higher dose of naloxone questionable. Table 1 shows available therapies for known or suspected opioid overdose.

Table 1: Available Therapies for Known or Suspected Opioid Overdose

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed)
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Narcan (generics available)	Complete or partial reversal of opioid depression	1971	Injection, available for IV, IM, and SC in three concentrations: 0.02mg, 0.4mg, and 1mg	Onset of action is apparent within two minutes	• Narcan in postoperative patients may cause agitation • Narcan should be used with caution in patients with pre-existing cardiac disease	Approved for use in the entire pediatric age range
EVZIO (Naloxone HCI)	Emergency treatment of known or suspected opioid overdose	2014	Injection IM or SC, 2 mg/0.4 ml naloxone hydrochloride solution in a pre-filled autoinjector	Onset of action is apparent within two minutes	• Naloxone may cause an abrupt and complete reversal of opioid effects leading to withdrawal symptoms	The safety and effectiveness for both IM and SC have been established in pediatric patients of all ages
Narcan Nasal Spray	Complete or partial reversal of opioid reversal	2015	Nasal Spray: 2mg and 4mg of naloxone hydrochloride in 0.1 mL	Onset of action is apparent within two minutes	•Risk of recurrent respiratory and CNS depression •Precipitation of severe opioid withdrawal	Approved for use in the entire pediatric age range

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed)
Nalmefene hydrochloride (generics available)	Complete or partial reversal of opioid drug effects and management of known or suspected opioid overdose	Approved in 1995, discontinued in 2014 not for safety or efficacy reasons	Nalmefene HCL injection, For management of known or suspected opioid overdose – 1 mg/ml initial dose for non-opioid dependent patients is 0.5 mg/70 kg, may be followed with second dose of 1 mg/70 kg 2-5 minutes later	IV:0.5 to 2.0 mg in postoperative pain, Reversal of respiratory depression within 2 to 5 minutes IM/SC: I mg Reversal of presumed opioid overdose Effective within 5-15 minutes nalmefene has longer duration of action than naloxone at fully reversing doses	Cardiovascular risks with narcotic antagonist Risk of precipitated withdrawal	Safety and effectiveness of Nalmefene in pediatric patients have not been established. Safety and effectiveness of Nalmefene in neonates have not been established in clinical studies in neonates. Nalmefene (nalmefene hydrochloride injection) should only be used in the resuscitation of the newborn when, in the opinion of the treating physician, the expected benefits outweigh the risks.

4. Regulatory Background

4.1. U.S. Regulatory Actions and Marketing History

Naloxone HCL was first approved in 1971 (Narcan, NDA 013636), for intravenous, intramuscular, and subcutaneous administration for treatment of opioid overdose symptoms for use in adults and pediatric patients. The current labeling of Narcan recommends an initial dose of 0.4 mg to 2 mg, followed by repeat doses up to 10 mg in the setting of suspected opioid overdose. Narcan has been discontinued from marketing, however the Agency determined that it was not withdrawn from sale for reasons of safety or effectiveness (74 FR 22751) and there are generic naloxone products available. The off-label use of commercially available generic naloxone hydrochloride by the intranasal route of administration using a nasal atomizer has been growing in popularity to address the public health crisis in the United States.

The first product approved to address the risk of opioid overdose in a community setting was Evzio (Naloxone HCL injection), approved on April 3, 2014. Evzio (NDA 205787) in an autoinjector that delivers 0.4 mg of naloxone in 0.4 mL to the subcutaneous or intramuscular space. A higher dose version, Evzio 2 mg (NDA 209862) was approved on October 19, 2016. Narcan nasal spray (NDA 208411) was approved on November 18, 2015 and consists of a single-dose device of 4mg dose naloxone in 0.1 ml. Narcan nasal spray 2 mg strength was approved on January 24, 2017, but manufacturer has not marketed the 2 mg product.

4.2. Summary of Presubmission/Submission Regulatory Activity

Insys Development Company, Inc. was developing a nasal formulation of naloxone, a needle-free solution to treat known or suspected opioid overdose. The Applicant conducted the clinical development program under two INDs: IND 126,173 and IND 134,954. The company has been previously developing similar products under both INDs. Nasal (b) (4) routes were studied under IND 126173. Insys initially conducted a pilot study (INS012-16-079) using an exploratory Naloxone spray formulation at 8 and 16 mg single dose (b) (4) (b) (4) compared to Naloxone intramuscular injection 0.4 mg single dose in 30 healthy volunteers. The Cmax for the 16 mg intranasal formulation was much higher compared to the maximum approved Naloxone dose, 2 mg IV.
The End-of-Phase 2 meeting for IND 126173 took place on September 6, 2016 and the Agency expressed the following concerns:

- Division questioned the feasibility (b) (4) (b) (4)

[redacted] of the instructions may result in confusion in the emergency setting.
- The design of the device was not appropriate for intranasal (IN) administration.
- Properly designed Human factors testing is required
- Inclusion of nasal cavity assessment and olfactory function testing

In addition, evaluation of the impact on olfaction via detailed examination of the olfactory nerve testing and inclusion of smell test prior to and after dosing at appropriate intervals were requested by the Division and communicated to the Sponsor via email dated June 27, 2017.

[redacted]. The company selected the 8 mg intranasal dose including two formulations containing 20% and [redacted]% of alcohol for subsequent pivotal clinical pharmacology studies in comparison with Narcan (NDA 016636). Both formulations were studied under IND 134954.
Insys completed two comparative PK studies to support referencing the previous findings of efficacy and safety for Narcan injection.
The first study, INS012-17-108 was conducted to compare the pharmacokinetics of the Naloxone nasal spray 8 mg containing 20% and [redacted]% of alcohol with reference product Naloxone 0.4 mg IM in healthy volunteers.
The second study, INS012-18-119 was conducted per FDA recommendation during the Type C meeting for safety justification to compare Naloxone PK of the test nasal spray formulation with the maximum naloxone dose from injectable naloxone, IV 2 mg.
The Agency communicated the following issues to the Applicant during a Type C meeting for IND 134954 on February 22, 2018:

- The PK data generated from INS012-17-108 study for both formulations appear to be much higher than the 0.4mg IM dose and demonstrate that both formulations meet the exposure standard for approval of community-use naloxone products.
- The [redacted]% alcohol formulation had much higher systemic exposure based to the PK results compared to the listed drug. However, it was unclear if there would be clinically significant difference in reversing an overdose even if the product demonstrated a slightly faster onset of action, as the onset of approved naloxone products is very rapid.
- The Division reiterated that olfactory function testing is required in this development program because of the higher proposed doses and the presence of ethanol, which is potentially neurotoxic, in the proposed formulations.

In the response to the Initial pediatric study plan (iPSP) submitted on June 19, 2018, Insys submitted a pediatric assessment plan with NDA and addressed the following issues:
- The safety and effectiveness of the proposed dose of naloxone for all pediatric age ranges, including neonates.

- Why the absorption of the drug through the nasal mucosa will be different in pediatric patients, including neonates, compared to adults.
- Justification for the proposed dose volume in al pediatric patients, including neonates.
- A device that can appropriately deliver the correct volume to all pediatric patients, including neonates.
- The nasal actuator tip is appropriately sized for and can appropriately deliver the correct volume to all pediatric patients, including neonates.

The Agreed iPSP addressed the identified issues, was submitted October 31, 2018 and was accepted by the Division with no further comments. The application was discussed at the Pediatric Review Committee (PeRC) meeting on November 28, 2018 and PeRC agreed with the Sponsors plan for an assessment for the entire pediatric age group as outlined in the Agreed iPSP.

IND 134954 for the proposed 8 mg Naloxone nasal spray formulation was denied Fast Track designation (FTD) twice, on September 20, 2018 and on February 20, 2019, because there were not data provided to demonstrate that the product had the potential to address an unmet medical need. A higher naloxone exposure alone was not sufficient to support the FTD, because there were no data provided to establish the need for or benefit of higher exposures compared to available therapies.
On September 3, 2019 The Applicant communicated to the FDA about change of the ownership from Insys to Hikma Pharmaceuticals USA Inc (Hikma).

4.3. Foreign Regulatory Actions and Marketing History

There is no foreign marketing development for Naloxone nasal spray.

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

5.1. Office of Scientific Investigations (OSI)

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted for the PK studies INS012-17-108 and INS012-18-119.

5.2. Product Quality

The final CMC review is pending at this time. The Applicant changed from (Hikma) during the review cycle. With transfer of ownership, an inspection of the new site by the Agency is required. A new facility was identified by the Applicant during the review cycle as a result of change in application ownership from Insys to Hikma Pharmaceuticals USA Inc. However, since the new facility will not be ready for the inspection until June 30, 2020, a complete response has been tentatively recommended by CMC.

5.3. Clinical Microbiology

Not applicable.

5.4. Nonclinical Pharmacology/Toxicology

The final pharmacology/toxicology review is pending at this time.

5.5. Clinical Pharmacology

Dr. Wei Qiu's final Clinical Pharmacology review is pending at this time. The preliminary conclusion reached by the clinical pharmacology reviewer are that there are no outstanding clinical pharmacology issues that preclude approval.

The Applicant conducted two comparative bioavailability studies submitted in support of the Naloxone 8 mg containing 20% of alcohol, which is the only formulation proposed for marketing in this application.

1. Study INS012-17-108 was an open-label, randomized three treatment, six-sequence, three-way, crossover study in 24 adult male and female healthy volunteers. The treatment arms were:
    - Treatment A: Naloxone nasal spray, 8 mg/spray (20% alcohol)
    - Treatment B: Naloxone nasal spray, 8 mg/spray ((b) (4)% alcohol)
    - Treatment C: Naloxone HCL IM injection, 0.4 mg/mL

2. Study INS012-18-119 was randomized, open-label, single-dose, four-treatment, four-way, crossover study in 24 adult male and female healthy volunteers. The study arms were:
    - Treatment A: Naloxone nasal spray, 8 mg/spray (20% alcohol)
    - Treatment B: Naloxone nasal spray, 8 mg/spray ((b) (4) alcohol)

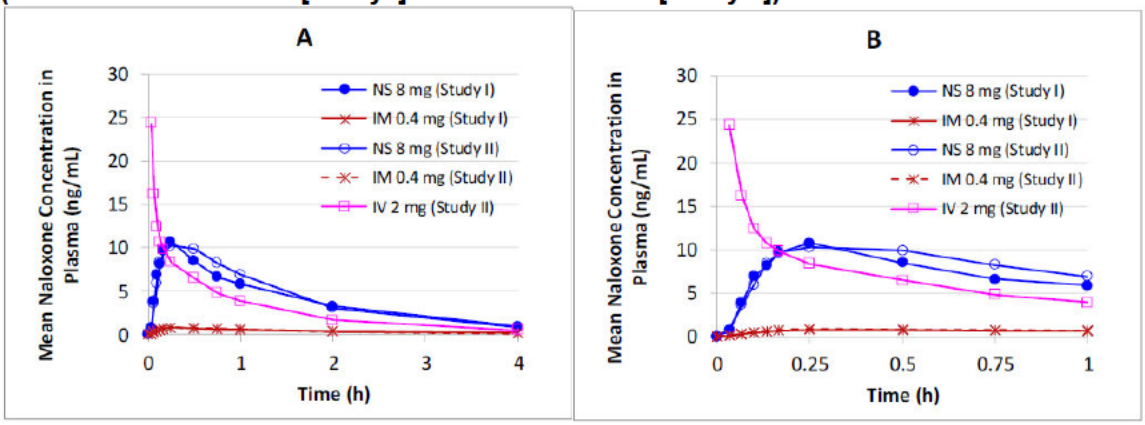
- Treatment C: Naloxone HCL IM injection, 0.4 mg/mL
- Treatment D: Naloxone HCL Intravenous (IV) injection, 2 mg (1 mg/mL)

Table 2: Mean Plasma Concentration of Unconjugated Naloxone Through 1 Hour After Administration of Naloxone Nasal Spray 8 mg, 20% Alcohol (Treatment A), Naloxone Nasal Spray 8 mg, (b)(4)% Alcohol (Treatment B), and Naloxone HCL IM Injection 0.4 mg (Treatment C)

Treatment Description	n	2 min Mean	4 min Mean	6 min Mean	8 min Mean	10 min Mean	15 min Mean	30 min Mean	45 min Mean	60 min Mean
Naloxone Nasal Spray 8 mg (20% alcohol)	24	0.725	3.84	6.87	8.07	9.64	10.7	8.44	6.59	5.83
Naloxone Nasal Spray 8 mg ((b)(4)% alcohol)	24	2.77	11.8	21.3	22.6	25.8	23.9	15.4	11.1	9.06
Naloxone HCL IM Injection 0.4 mg	24	0.0527	0.241	0.420	0.547	0.660	0.792	0.699	0.628	0.570

Source: Clinical study report Table 7.

Figure 1: Mean Plasma Concentration Profiles of Unconjugated Naloxone Following a Single Dose of Naloxone Nasal Spray 8 mg Containing 20% Alcohol (NS 8 mg) versus 0.4 mg IM Injection (IM 0.4 mg) and 2 mg IV Injection (IV 2 mg) in Healthy Subjects (Panel A: 0 – 4 h and Panel B: 0 – 1 h) (Studies INS012-17-108 [Study I] and INS012-18-119 [Study II])



Source: Clinical Study report Figure 4.

Table 3: Mean (CV%) Plasma Pharmacokinetic Parameters of Total Naloxone (INS012-17-108)

Treatment	A	B	C
Formulation/ Route	Naloxone Nasal Spray (20% alcohol)	Naloxone Nasal Spray (b) (4)% alcohol)	Naloxone IM (0.4 mg/mL)
Dose (mg)	8	8	0.4
N	24	24	24
C_{max} (ng/mL)	46.5 (51.2) [41.6]	49.2 (37.8) [46.0]	1.49 (30.3) [1.43]
T_{max} (h)[a]	1.00 (0.250 – 4.00)	0.375 (0.133 – 1.00)	0.500 (0.133 – 2.00))
AUC_{last} (ng•h/mL)	128 (29.8) [123]	119 (31.3) [114]	4.91 (25.5) [4.78]
$AUC_{0\text{-}inf}$ (ng•h/mL)	137 (29.9) [132][b]	124 (34.2) [118][c]	5.30 (27.4) [5.13][d]
$t_{1/2}$ (h)	6.10 (18.8) [5.99][b]	5.63 (17.3) [5.55][c]	2.91 (24.4) [2.83][d]
F_{rel} (%)[e]	129	115	100

[a] Reported as median (min - max)
[b] N=19, [c] N=18, [d] N=19 representing the number of subjects for which log-linear terminal phase could be determined
[e] F_{rel} (%) = Geometric mean $AUC_{0\text{-}inf}$ (test) / Geometric mean $AUC_{0\text{-}inf}$ (reference) × 100%, representing relative bioavailability of the two test Naloxone Nasal Spray formulations to the reference formulation Naloxone IM 0.4 mg

Source: Synopsis of individual studies, table 13.

The Applicant relied upon two comparative bioavailability studies and literature review that was non-product specific, in support of this application to establish scientific bridge to their NDA for Narcan (NDA 16636) in order to establish the safety and efficacy of Narcan nasal spray.

Two comparative bioavailability studies were conducted to demonstrate that Naloxone nasal spray 8 mg would provide comparable or higher exposure (e.g., Cmax, AUC last, and AUCinf, and higher of higher exposure during the early absorption phase (e.g., naloxone concentration at 2 to 5 min post dose) in comparison to the reference product at the tested dose of 0.4 mg via IM injection.

The 8 mg Narcan with 20% alcohol demonstrated higher systemic exposure to naloxone, in comparison to the 0.4 mg IM dose, including earlier time points (i.e., 2, 4, 6, 8, 10 minutes post dose), 14-fold greater Cmax, and 10-fold greater AUCs, which provides an adequate scientific bridge to the previous finding of efficacy for Narcan injection.

In addition, comparison with 2 mg IV injection was made to support safety of the Naloxone exposure. The Cmax of the 8 mg Narcan with 20% alcohol did not exceed that of the 2 mg IV injection, but the corresponding AUClast and AUC0-inf values were 42 and 48% greater than a single 2 mg IV injection. The PK data in these studies are not sufficient to rely fully on the previous finding of safety of Narcan injection.

The frequency and the timing for the blood samples were adequate. I concur with the preliminary conclusions reached by the clinical pharmacology reviewer. There are no outstanding clinical pharmacology issues that preclude approval.

5.6. Devices and Companion Diagnostic Issues

The Center for Devices and Radiologic Health (CDRH) recommended a complete response letter be issued to the Applicant due to outstanding deficiencies related to the device constituent.

5.7. Consumer Study Reviews

Hikma is planning to submit the results of the Human factor (HF) study at the end of March 2020, and these results will not be reviewed during this review cycle.

6. Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Table 4: **Listing of Clinical Trials Relevant to This NDA**

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
INS012-17-108	NCT03827629	Phase 1, randomized, open-label, single-dose, three treatment, six-sequence, three-way, comparative bioavailability, crossover study	• One dose of 8 mg Naloxone nasal spray containing 20% alcohol • One dose of 8 mg Naloxone nasal spray containing (b)(4)% alcohol • Single dose of Naloxone HCL IM 0.4 mg/mL	N/A No safety endpoints defined	Three single doses were administered with a 4-day washout period between each dose Last PK and nasal exam performed 24 h after the dosing, olfactory nerve assessment done approximately 24 hours	N=24	Healthy volunteers	Single center in United States
INS012-18-119	NCT03827642	Phase 1, randomized, open-label, single-dose, four-treatment, four-way, comparative bioavailability, crossover study	• Single dose of Naloxone nasal spray 8 mg in 20% alcohol • Single dose Naloxone nasal spray in (b)(4)% alcohol • 2 mg of Naloxone HCL, IV injection	N/A No safety endpoints defined	Single dose in each of the four treatment periods with washout period of 4 days between two periods	N=24	Healthy volunteers	Single center in United States

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
INS012-16-079	Was not registered on clinicaltrials.gov	Phase 1, randomized, open-label, single-dose, five-treatment, comparative bioavailability, crossover study	• 16 mg of Naloxone spray administered intranasally • 16 mg of Naloxone spray administered sublingually • 8 mg of Naloxone spray administered intranasally • 8 mg of Naloxone spray administered sublingually • 0.4 mg/ml of Naloxone HL IM injection		Five single doses were administered with a 4-day washout period between each dose 2 hours	N=30	Healthy volunteers	Single center in United States

Source: reviewer generated

6.2. Review Strategy

This NDA review focused on review of two PK studies submitted by the Applicant to support marketing approval. The clinical development program focused on establishing the PK and safety characteristics of the drug product. The Division has determined the path for the clinical development of novel naloxone product, which consists of two PK studies.

1. Study INS012-17-108 demonstrating comparable or greater systemic exposure to naloxone with the new naloxone product, particularly in the early critical period after drug administration in healthy volunteers.
2. Study INS012-18-119 was recommended by the Division and was completed to justify the safety by comparison between proposed naloxone nasal spray to the approved maximum naloxone dose, injectable naloxone IV, 2 mg.

Key safety data from both studies are presented in Section 8, Safety.
Study INS012-16-079 was dose exploratory study that did not study the product to be marketed. Thus, the study INS012-16-079 was not reviewed in detail.

Since the new product is planned to be used intranasally, particular attention was paid to the nasal examination, nasal symptoms, and olfactory nerve assessment results.

7. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant utilized the 505(b)(2) pathway, relying on the Agency's previous efficacy and safety findings for the naloxone product, 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 the new naloxone product, particularly in the early critical period after drug administration.

7.1. Study INS012-17-108: Phase 1, open-label, randomized, crossover, comparative bioavailability study of Naloxone nasal spray and Naloxone Hydrochloride intramuscular injection in 24 healthy volunteers.

7.1.1. Study Design

Objectives

Primary objective: to compare early exposures (plasma concentration at each time point and partial AUCs) up to 1 hour following a single dose of two test formulations of Naloxone nasal spray (8mg containing 20% alcohol and 8mg containing (b)(4)% alcohol) with the reference formulation of Naloxone Hydrochloride (HCL) intramuscular injection (0,4mg/mL) under fasting conditions.

Secondary objectives:

- To compare the bioavailability of the test formulation of a single dose of 8 mg containing 20% alcohol Naloxone nasal spray and 8 mg containing (b)(4)% alcohol of Naloxone nasal spray to a single dose of Naloxone HCL IM (0.4mg/mL) under fasting conditions.
- To evaluate the safety and tolerability of naloxone nasal spray.

Location: Worldwide clinical trials, San Antonio, Tx

Duration: Three single doses were administered with a 4-day washout period between each

dose.

Population: Healthy adult volunteers

Inclusion and Exclusion criteria: The enrolled population was otherwise healthy adult volunteers, not pregnant, aged 18-45 years of age inclusive.

Key Exclusion criteria include:

- Presence of nasal cavity piercings
- Presence of polyps or unilateral or bilateral abnormalities of the nares, nasal turbinates, or septum (including deviated septum).
- Subject has chronically used nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids within 30 days prior to Day 1.
- Any subject with reported smell disturbances and any reduction of smell regardless of cause at screening based on the Brief Smell Identification Test (BSIT).

Reviewer comments: The population enrolled was appropriate for the study.

Treatments:

Treatment A:

Naloxone nasal spray, 8 mg/spray (20% alcohol)

Dose: 8 mg, intranasal administration

Treatment B:

Naloxone nasal spray, 8 mg/spray (b) (4)% alcohol)

Dose: 8 mg, intranasal administration

Treatment C:

Naloxone HCL IM injection, 0.4 mg/mL

Dose: 0.4 mg, IM injection

Trial Design

Phase 1, randomized, open-label, single-dose, three treatment, six-sequence, three-way, comparative bioavailability, crossover study. Safety assessments included vital signs (Seated blood pressure, pulse rate, respiration rate, and temperature), ECGs, physical examination, nasal cavity examination, nasal irritation examination, olfactory function testing (BSIT), injection site assessment, clinical laboratory tests including hematology (Hb, Hct, leukocyte count, RBCs, and platelet count), blood chemistry (albumin, BUN, creatinine, total bilirubin, ALP, AST, ALT, sodium, potassium, chloride, LDH, uric acid, glucose, and calcium), UA, serology, B surface Ag, Hepatitis C Ab, and HIV; pregnancy screen, concomitant medications, drug screen, and AE assessments.

The study consisted of four periods, a screening period and three treatment periods.

Table 5: Treatment Sequences

Sequence (n=4 Subjects Per Sequence)	Treatment Periods		
	Period 1	Period 2	Period 3
A-B-C	A	B	C
B-C-A	B	C	A
C-A-B	C	A	B
A-C-B	A	C	B
C-B-A	C	B	A
B-A-C	B	A	C

Source: Clinical study report, table 2.

Treatment A: Naloxone Nasal spray, 8 mg (containing 20% alcohol) of naloxone hydrochloride per spray nasal administration

Dose = 8 mg (8 mg of naloxone hydrochloride per spray)

Treatment B: Naloxone Nasal Spray, 8 mg (containing (b) (4)% alcohol) of naloxone hydrochloride per spray, nasal administration

Dose = 8 mg (8 mg of naloxone hydrochloride per spray)

Treatment C: Naloxone HCL IM Injection, 0.4 mg/mL

Dose = 0.4 mg (1 mL)

During each treatment period, 10 mL blood samples were obtained for unconjugated naloxone and total naloxone analysis before and after each dose at 0 (pre-dose), 2, 4, 6, 8, 10, 15, 30, and 45 minutes, and at 1, 2, 4, 8, 12 and 24 hours post dose. A total of 45 PK blood samples were collected from each subject and 15 samples in each study period.

Reviewer comment: The frequency and the timing for the blood sample were adequate. The results of the PK studies results did not raise any new safety concerns.

Table 6: Schedule of Assessments

Assessment/ Procedure	Screening Period	Period 1			Period 2		Period 3	EOS/Early Withdrawal[a]
		Check-In: Day -1	Days 1-2	Washout Days 3-4	Days 5-6	Washout Days 7-8	Days 9-10	Day 10
Written informed consent	X							
Inclusion/exclusion assessment	X	X						
Medical history and demographics	X							
Concomitant medication use	X	X	X	X	X	X	X	X
Vital signs[b]	X		X		X		X	
12-lead ECG	X							X
Physical examination	X							X
Nasal cavity examination[c]	X	X						X
Nasal irritation examination[d]			X		X		X	
Clinical laboratory tests	X							X
Urine drug, alcohol, and cotinine screens	X	X						
Serology	X							
Pregnancy test (all female subjects)[e]	X	X						X
FSH test (postmenopausal subjects)	X							
Medical history update		X						
Randomization			X					

Study treatment administration[f]			X		X		X	
PK sample blood draws[g]			X		X		X	
AE assessments[h]			X	X	X	X	X	X
Meals[i]		X	X	X	X	X	X	
Injection site assessment[j]			X		X		X	
Olfactory function test (BSIT)[k]	X	X	X		X		X	X
Subjects in confinement		X	X	X	X	X	X	

Source: Clinical study report, table 3.

Nasal cavity examination

The investigator will perform a nasal cavity examination for all the subjects at screening, Day 1 and at the end of study/early discontinuation visit. The nasal cavity will be inspected with an otoscope from the front to anterior nares using the form presented below.

Nasal irritation examinations were performed prior to dosing, 5 and 30 minutes, and at 1,4, and 24-hours post dose.

Figure 2: Nasal Cavity Examination

NASAL CAVITY EXAMINATION		**[ ] NORMAL**		**[ ] ABNORMAL**	
Assessment Finding	**Nostril**	**Present**	**Not Present**	**If Abnormal**	**Comments**
Polyps	Left	☐	☐	☐ NCS or ☐ CS	
	Right	☐	☐	☐ NCS or ☐ CS	
Unilateral or bilateral abnormality of the nares, nasal turbinates, or septum (including deviated septum)	Left	☐	☐	☐ NCS or ☐ CS	
	Right	☐	☐	☐ NCS or ☐ CS	
Active infection	Left	☐	☐	☐ NCS or ☐ CS	
	Right	☐	☐	☐ NCS or ☐ CS	
	Left	☐	☐	☐ NCS or ☐ CS	

Viral lesions	Right	☐	☐	☐ NCS or ☐ CS	
Nasal irritation/inflammation (redness, swelling, rhinorrhea, congestion)	Left	☐	☐	☐ NCS or ☐ CS	
	Right	☐	☐	☐ NCS or ☐ CS	
Nasal cavity or nose piercing	Left	☐	☐	☐ NCS or ☐ CS	
	Right	☐	☐	☐ NCS or ☐ CS	
Evidence of prior nasal cavity or nose piercing	Left	☐	☐	☐ NCS or ☐ CS	
	Right	☐	☐	☐ NCS or ☐ CS	
Other (Specify _____)	Left	☐	☐	☐ NCS or ☐ CS	
	Right	☐	☐	☐ NCS or ☐ CS	
				☐	

Source: Protocol INS012-17-108, 17.2 Appendix 2.

Nasal Irritation Scale

The Investigator will perform a nasal irritation assessment based on the scale below at 0 (predose), 5 and 30 minutes at 1,4, and 24 hours postdose.

Figure 3: Nasal Irritation Scale

NASAL IRRITATION SCALE				
Nostril	**Nasal Irritation Score**		**If Abnormal**	**Comments**
RIGHT	☐	0 - None		
	☐	1 – Inflamed mucosa, no bleeding	☐ NCS or ☐ CS	
	☐	2 – Minor bleeding which stops within 1 minute		
	☐	3 – Minor bleeding, taking 1-5 minutes to stop		
	☐	4 – Substantial bleeding for 4-60 minutes, does not require medical intervention		

	☐	5 – Ulcerated lesions, bleeding which requires medical intervention		
LEFT	☐	0 - None		
	☐	1 – Inflamed mucosa, no bleeding		

Source: Protocol INS012-107-108, 17.2 Appendix 2.

Olfactory function test:

All subjects underwent an olfactory function test (via Brief Smell Identification test, BSIT) at screening, Day 1, prior to first dose, and at the end of the study. Additionally, subjects assigned to Naloxone nasal spray, 8 mg containing 20% alcohol (Treatment A) and (b)(4)% alcohol (Treatment B), underwent an olfactory test prior to dosing and at approximately 24 hours post dose.

The BSIT included 12 odorants on scent strips. The scent was released when the strips were scratched with a pencil tip. The subjects were handed a multiple-choice questionnaire and asked to identify which smell corresponded to the scent trip for each odorant.

The olfactory score via the BSIT was defined as the number of odorants correctly identified out of 12 tested. A higher score corresponded to better olfactory performance, and abnormal olfactory function was defined as correctly identifying fewer than nine odorants.

Study Endpoints
Not applicable.

Statistical Analysis Plan
The clinical pharmacology team reviewed the statistical analysis plan. Refer to the clinical pharmacology review of Wei Qiu, PhD with concurrence from Yun Xu, PhD for more details.

Protocol Amendments

There were few Information Request letters sent to the Applicant with clarifying questions mostly related to the CMC. There were no significant study modifications or amendments submitted that would affect the safety measurements and assessments.

7.1.2. Study Results +

Compliance with Good Clinical Practices

The Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and 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.

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. A total of 8 investigators were listed in both studies.

Patient Disposition

In Study INS012-17-108 of the 24 subjects enrolled, 24 subjects (100%) completed the study.

Protocol Violations/Deviations

There were no major protocol deviations.

In Study INS012-17-108 I identified 23 subjects (95.8%) had a study procedure performed outside the assessment window and 9 subjects (37.5%) had a missed assessment. There were twenty-three nasal irritation assessments performed late. For four subjects the assessment was performed with more than an hour late and for the rest they were performed less than one hour late. There were nine olfactory function assessment tests performed early. For four subjects the test was completed more than one hour early.

In Study INS012-108-119 I identified three main categories of protocol deviations in performing nasal irritation exam (24), olfactory function test (9), and blood sampling (25). Reported protocol deviations were due to assessments performed outside of the assessment window

including nasal irritation exams performed with range of 3 minutes to hour and a half being late, olfactory function tests performed early ranging between 30 minutes and hour and a half, and blood sampling that were mostly due to the difficult access and staff errors.

Reviewer comment: The Applicant reported that there were minor protocol deviations mainly resulting from procedures performed outside of the clinical study protocol-specified time window and were mostly due to staff errors. I agree with the conclusion Applicant made. Deviations are minor and do not raise any safety concerns.

Demographic Characteristics

The demographics for studies INS012-17-108 and INS012-18-119 were similar. The subjects were mostly white non-Hispanic/Latino (58.3% and 62.5% for studies 108 and 119, respectively) with a mean age of 29 and 33.3 respectively, a mean weight of 70.83 and 78.97 respectively, and a mean height of 165.87 cm and 173.50 cm respectively. There were more female than males (62.5% vs. 37.5%) in INS012-17-108 and more males than females (58.3% vs.41.7%) in INS012-18-119.

Reviewer comment: See the clinical pharmacology review for a discussion of the adequacy of the population studied for the purpose of establishing a scientific bridge to Narcan injection.

Other Baseline Characteristics (e.g., disease characteristic, important concomitant drug)
There were no other baseline important characteristics for this product.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not applicable.

Efficacy Results – Primary Endpoint

Not applicable.

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.

7.2. Study INS012-18-119:

7.3. Title: Phase 1, open-label, randomized, crossover, comparative bioavailability study of Naloxone nasal spray and Naloxone hydrochloride intravenous and intramuscular injection in healthy volunteers.

7.3.1. Study Design

Objectives:

Primary objectives:

- To assess PK following a single dose of two test formulations of Naloxone nasal spray, 8 mg (containing 20% and (b)(4)% alcohol) and reference formulations of Naloxone HCL intravenous (IV) injection 2 mg and Naloxone HCL IM injection, 0.4mg under fasting conditions.
- To compare the bioavailability of the tested formulations of Naloxone nasal spray with the reference formulations of Naloxone IV and IM injections.

Secondary objectives:

- To compare early exposures (plasma concentrations at each time point and partial areas under the curve, AUCs) up to 2 hours following a single dose of two
- Naloxone spray formulations, 8 mg containing 20% and (b)(4)% alcohol to a single dose of 2mg Naloxone HCL IV injection and single dose of Naloxone HCL IM injection, 0.4mg/mL under fasting conditions.
- To evaluate the safety and tolerability of Naloxone nasal spray

Location: Worldwide clinical trials, San Antonio, Tx

Duration: Single dose in each of the four treatment periods with washout period of four days between two period.

Inclusion and Exclusion criteria: The enrolled population was otherwise healthy adult volunteers, not pregnant, aged 18-45 years of age inclusive**.**
Key Exclusion criteria include:

- Presence of nasal cavity piercings
- Presence of polyps or unilateral or bilateral abnormalities of the nares, nasal turbinates, or septum (including deviated septum).
- Subject has chronically used nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids within 30 days prior to Day 1.
- Any subject with reported smell disturbances and any reduction of smell regardless of cause at screening based on the Brief Smell Identification Test (BSIT).

Reviewer comments: The population enrolled was appropriate for the study.

Treatments:

Treatment A:
Naloxone nasal spray, 8 mg/spray (20% alcohol)
Dose: single dose 8 mg (1 spray), intranasal administration

Treatment B:
Naloxone nasal spray, 8 mg/spray ((b) (4) % alcohol)
Dose: single dose 8 mg (1 spray), intranasal administration

Treatment C:
Naloxone HCL IM injection, 0.4 mg/mL
Dose: single dose 2 mg (2 ml), IV injection

Treatment D:
Naloxone HCL Intravenous (IV) injection, 2 mg (1 mg/mL)
Dose: single dose 0.4 mg (1 ml, IM injection

Study design: Phase 1, randomized, open-label, single-dose, three treatment, six-sequence, three-way, comparative bioavailability, crossover study. Safety assessments included vital signs (Seated blood pressure, pulse rate, respiration rate, and temperature), ECGs, physical examination, nasal cavity examination, nasal irritation examination, olfactory function testing (BSIT), injection site assessment, clinical laboratory tests including hematology (Hb, Hct, leukocyte count, RBCs, and platelet count), blood chemistry (albumin, BUN, creatinine, total bilirubin, ALP, AST,ALT, sodium, potassium, chloride, LDH, uric acid, glucose, and calcium), UA,

serology, B surface Ag, Hepatitis C Ab, and HIV; pregnancy screen, concomitant medications, drug screen, and AEs assessments.

The study consisted of four periods, a screening period and three treatment periods.

Table 7: Treatment Sequences

Sequence (n=6 subjects per sequence)	Treatment Periods			
	Period 1	Period 2	Period 3	Period 4
A-D-C-B	A	D	C	B
B-C-D-A	B	C	D	A
C-A-B-D	C	A	B	D
D-B-A-C	D	B	A	C

Treatment A: Naloxone Nasal Spray, 8 mg (containing 20% alcohol) of naloxone hydrochloride per spray, nasal administration. Dose = 8 mg (8 mg of naloxone hydrochloride per spray). Insys Development Company, Inc.
Treatment B: Naloxone Nasal Spray, 8 mg (containing (b) (4)% alcohol) of naloxone hydrochloride per spray, nasal administration. Dose = 8 mg (8 mg of naloxone hydrochloride per spray). Insys Development Company, Inc.
Treatment C: Naloxone HCL IV Injection, 2mg (1 mg/mL) Dose = 2mg (2 mL). Distributed by Hospira, Inc.
Treatment D: Naloxone HCL IM Injection (0.4mg/mL) Dose = 0.4mg (1 mL). Distributed by Hospira, Inc.

Source: Protocol INS012-18-119 Appendix 16.1.1, table 1

During each treatment period, 10 mL blood samples were obtained for unconjugated naloxone and total naloxone analysis before and after each dose at 0 (pre-dose), 2, 4, 6, 8, 10, 15, 30, and 45 minutes, and at 1, 2, 4, 8, 12 and 24 hours post dose. A total of 45 PK blood samples were collected from each subject and 15 samples in each study period.

Reviewer comment: The frequency and the timing for the blood sample were adequate. The results of the PK studies results did not raise any new safety concerns.

Table 8:Schedule of Assessments

Assessment/ Procedure	Screening Period	Period 1			Period 2		Period 3	EOS/Early Withdrawal[a]
		Check-In: Day -1	Days 1-2	Washout Days 3-4	Days 5-6	Washout Days 7-8	Days 9-10	Day 10
Written informed consent	X							

Inclusion/exclusion assessment	X	X						
Medical history and demographics	X							
Concomitant medication use	X	X	X	X	X	X	X	X
Vital signs[b]	X		X		X		X	
12-lead ECG	X							X
Physical examination	X							X
Nasal cavity examination[c]	X	X						X
Nasal irritation examination[d]			X		X		X	
Clinical laboratory tests	X							X
Urine drug, alcohol, and cotinine screens	X	X						
Serology	X							
Pregnancy test (all female subjects)[e]	X	X						X
FSH test (postmenopausal subjects)	X							
Medical history update		X						
Randomization			X					
Study treatment administration[f]			X		X		X	
PK sample blood draws[g]			X		X		X	
AE assessments[h]			X	X	X	X	X	X

Assessment/ Procedure	**Screening Period**	**Period 1**			**Period 2**		**Period 3**	**EOS/Early Withdrawal[a]**
		Check-In: Day -1	**Days 1-2**	**Washout Days 3-4**	**Days 5-6**	**Washout Days 7-8**	**Days 9-10**	**Day 10**

Meals[i]		X	X	X	X	X	X	
Injection site assessment[j]			X		X		X	
Olfactory function test (BSIT)[k]	X	X	X		X		X	X
Subjects in confinement		X	X	X	X	X	X	
Discharge from study								X

[a] Procedures will be performed on the day of the final blood draw or at early withdrawal.
[b] Vital signs (seated blood pressure, pulse rate, body temperature, and respiration rate) will be measured at screening, prior to dosing, at end of study/early termination and at approximately the following time points: 1, 2, 4, and 24 hours post-dose, and at any other time deemed medically necessary. Vital signs will be measured after the subject has been sitting for at least 3 minutes. [c] All subjects will undergo a nasal cavity examination at screening, check-in, and end-of-study/Early withdrawal.
[d] All subjects randomized to Naloxone Nasal Spray, 8 mg containing 20% alcohol (Treatment A) and Naloxone Nasal Spray, 8 mg containing (b) (4)% alcohol (Treatment B) will undergo a nasal irritation examination at 0 (pre-dose), 5, and 30 minutes and at 1, 4, and 24 hours post dose.
[e]Serum βhCG pregnancy test at screening; urine pregnancy tests at check-in and at end of study.
[f] Dose-schedule: Subjects will receive study drug following a supervised overnight fast of at least 10 hours.
[g] Blood samples for unconjugated and total naloxone analyses will be collected at 0 (pre-dose), 2, 4, 6, 8, 10, 15, 30, and 45 minutes, and at 1, 2, 4, 8, 12- and 24-hours post-dose (15 time points). The pre-dose blood samples will be collected within 60 minutes prior to dosing.
[h] Treatment-emergent AE monitoring begins with the first dose of study medication.
[i] Standard meals will be provided at specified times during confinement periods.
[j] An injection site assessment will be performed for subjects randomized to receive the IM injection prior to dosing and approximately 1 hour following dose.
[k] All subjects will undergo an olfactory function test (BSIT) at screening, check-in on Day -1, Period 1, prior to first dose in Period 1, and at end-of-study/early withdrawal. Additionally, subjects assigned to Naloxone Nasal Spray, 8 mg containing 20% alcohol (Treatment A) and Naloxone Nasal Spray, 8 mg containing (b) (4)% alcohol (Treatment B), will undergo an olfactory function test prior to dose on Days 5, 9, and 13 and at approximately 24 hours post dose on Days 2, 6, 10, and 14.
AE = adverse event; ECG = electrocardiogram; hCG = human chorionic gonadotropin; HCl = hydrochloride; PK = pharmacokinetics.

Source: Protocol number INS012-18-118, table 4.

Nasal cavity examination, nasal irritation examinations, and Olfactory function test were performed per schedule presented in Table 8. Details on assessments are described in section 6.1.1 of the review.

Study Endpoints
Not applicable

Statistical Analysis Plan

Protocol Amendments

7.3.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and 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.

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. A total of 8 investigators were listed in both studies.

Patient Disposition

In Study INS012-18-119 of the 24 subjects enrolled, 23 subjects (95.8%) completed the study. Subject (b) (6) was withdrawn by the Investigator on Day 9 of the study for use of ibuprofen for a tooth pain.

Reviewer comment: This subject was appropriately withdrawn from the study, because of use of the prohibited medication. I do not anticipate that withdrawal of one subject will affect the results.

Protocol Violations/Deviations

In Study INS012-108-119 I identified three main categories of protocol deviations in performing nasal irritation exam (24), olfactory function test (9), and blood sampling (25). Reported

protocol deviations were due to assessments performed outside of the assessment window including nasal irritation exams performed with range of 3 minutes to hour and a half being late, olfactory function tests performed early ranging between 30 minutes and hour and a half, and blood sampling that were mostly due to the difficult access and staff errors.

Reviewer comment: The Applicant reported that there were minor protocol deviations mainly resulting from procedures performed outside of the clinical study protocol-specified time window and were mostly due to staff errors. I agree with the conclusion Applicant made. Deviations are minor and do not raise any safety concerns.

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

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not applicable

Efficacy Results – Primary Endpoint

Not applicable

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

8. Integrated Review of Effectiveness

8.1. Assessment of Efficacy Across Trials

The Applicant utilized the 505(b)(2) pathway, relying on the Agency's previous efficacy and safety findings for naloxone product, Narcan (NDA 016636), and bridged to those findings by performing two comparative bioavailability studies. The Applicant evaluated the pharmacokinetic profile of Naloxone nasal spray 8mg, containing 20% alcohol in two open-label, randomized, single dose bioavailability studies in healthy volunteers. As previously discussed with the Division, the Applicant's clinical program consists of two PK studies:

- INS012-17-108: comparing the pharmacokinetics of the Naloxone nasal spray 8 mg containing 20% and (b)(4)% of alcohol with reference product Naloxone 0.4 mg IM in healthy volunteers;
- INS012-18-119: comparing Naloxone PK of the test nasal spray formulation with the maximum naloxone dose from injectable naloxone, IV 2.

Based on the review of comparative bioavailability studies showed comparable pharmacokinetics and met the requirements set forth by the Division. Therefore, the Applicant may rely on the Agency's previous findings of safety and efficacy for Narcan.

The applicant was required to support the safety and efficacy of Narcan nasal spray in pediatrics, based on the review of available information, including the published literature, clinical published guidelines, and the approved injectable labeling for Narcan. Because Narcan nasal spray represents a change in dosing regimen, the Applicant is required to conduct a pediatric assessment under the Pediatric Research Equity Act (PREA).

The pediatric assessment was required to have addressed the following issues:

- The safety and effectiveness of the proposed dose of naloxone for all pediatric age ranges, including neonates.
- Why the absorption of the drug through the nasal mucosa will be different in pediatric patients, including neonates, compared to adults.
- Justification for the proposed dose volume in al pediatric patients, including neonates.
- A device that can appropriately deliver the correct volume to all pediatric patients, including neonates.
- The nasal actuator tip is appropriately sized for and can appropriately deliver the correct volume to all pediatric patients, including neonates.

Refer to section 9.8.3 for additional details on the pediatric assessment.

8.1.1. Primary Endpoints

Not applicable.

8.1.2. Secondary and Other Endpoints

Not applicable

8.1.3. Subpopulations

Not applicable

8.1.4. Dose and Dose-Response

Not applicable

8.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable

8.2. Additional Efficacy Considerations

8.2.1. Considerations on Benefit in the Postmarked Setting

8.2.2. Other Relevant Benefits

8.3. Integrated Assessment of Effectiveness

9. Review of Safety

9.1. Safety Review Approach

Safety data in this application consisted of pooled data from PK Studies INS012-17-108 INS012-18-119 of review on the safety of Naloxone. I reviewed two PK studies submitted for systemic safety and local safety. I reviewed the integrated safety data, which summarized safety information from both studies. I closely reviewed adverse events data for any unexpected outcomes and safety data for any safety signals. Also, since the proposed dose for

Naloxone nasal spray is higher than other approved intranasal formulations and there is ethanol in the formulation, a main focus of the safety review was on nasal irritation and olfactory test results.

9.2. Review of the Safety Database

9.2.1. Overall Exposure

Overall, a total of 95 subjects were exposed to the two Naloxone nasal spray formulations in two PK studies. Forty-seven subjects received a single dose of Naloxone nasal spray 8 mg (containing 20% alcohol) and forty-eight subjects revived a single dose of Naloxone nasal spray, 8 mg (containing (b)(4)% alcohol). The formulation proposed for marketing is the 20% alcohol formulation.
Naloxone exposures from the two PK studies are summarized in the table below.

Table 9: **Subject Exposure in Naloxone Nasal Spray Pharmacokinetic Studies**

Study	Naloxone Nasal Spray 8 mg, 20% alcohol	Naloxone Nasal Spray 8 mg, (b)(4)% alcohol	Naloxone HCl IM 0.4 mg/mL (1 mL)	Naloxone HCl IV 2 mg (1 mg/mL)
INS012-17-108	24	24	24	n/a
INS012-18-119	23	24	23	24
Total exposure	47	48	47	24

Sources: CSR INS012-17-108, Listing 16.2.5.2; CSR012-18-119, Listing 16.2.5.2

Source: Summary of clinical safety, table 3.

9.2.2. Relevant characteristics of the safety population:

The Applicant included 95 healthy adult volunteers in two pharmacokinetic studies. Of these 95 volunteers, 47 healthy adult volunteers were exposed to the 8 mg nasal naloxone containing 20% of alcohol proposed by the Applicant.

9.2.3. Adequacy of the safety database:

Ninety- five subjects were included in the pharmacokinetics studies. The safety population consisted of randomized healthy adult population who received a single dose of study drug. Since the Applicant is utilizing the 505(b)(2) pathway and relying on the Agency's previous findings of Narcan, the exposure to 47 subjects to the proposed 8 mg nasal naloxone containing 20% alcohol from two pharmacokinetic studies is adequate for the purposes of this safety evaluation.

9.3. Adequacy of Applicant's Clinical Safety Assessments

9.3.1. 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.

9.3.2. Categorization of Adverse Events

Adverse events were coded by system organ class and preferred term based on the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary version 21.0 and summarized by system organ class (SOC) and preferred term within SOC. The definitions and categorizations provided by the Applicant of treatment-emergent adverse events and serious adverse events are acceptable.

9.3.3. Routine Clinical Tests

The clinical laboratory assessments in Study INS012-17-108 and Study INS012-18-119 consisted of hematology, chemistry, urinalysis, serology, at screening and final study visits. Drug and alcohol tests, and pregnancy testing in females of childbearing potential were performed at screening, baseline and final study visits. Blood sampling for pharmacokinetic analysis were collected for both Study INS012-17-108 and Study INS012-18-119.

Reviewer comment: The clinical laboratory testing from both studies were acceptable and provided some information to support the safety of using 8 mg Naloxone nasal spray. The nasal irritation assessment tool and monitoring are adequate to evaluate the potential for local toxicity.

9.4. Safety Results

9.4.1. Deaths

There were no deaths reported in these trials.

9.4.2. Serious Adverse Events

There were no serious adverse events (SAE).

9.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no study discontinuations in study INS012-17-108. One subject in study INS012-18-119 were terminated by the investigator on Day 9, because of use of ibuprofen for a toothache following Naloxone HCL IV injection, 2 mg.

Reviewer comment: Subject (b) (6) *was withdrawn from the study because of use of concomitant medication that was an exclusion criterion for the study. The event does not raise any safety concerns.*

9.4.4. Significant Adverse Events

The Applicant reported three adverse events under significant adverse events: one case of neutropenia and two cases of orthostatic hypotension. Both events were reported in study INS012-18-119. None were reported in study INS012-17-108.

Subject (b) (6), a 35-year old white male with no significant medical history experienced an episode of orthostatic hypotension approximately 10 minutes after receiving Treatment A (Naloxone nasal spray 8 mg, 20%). The HR at baseline was 61 and was recorded as 47 one hour after exposure to the study drug. The subject was put in Trendelenburg position and the adverse event resolved approximately 45 minutes later. The Investigator classified the adverse event as moderate in severity and unlikely to be related to the investigational drug. The subject experienced another episode of orthostatic hypotension on the same day approximately one hour after getting Treatment A. At baseline before study drug exposure the blood pressure (BP) was 121/75 mmHg. Repeated blood pressure done one hour later was 84/41 mmHg and 86/42 mmHg on repeat testing. Two hours later BP was recorded as 117/67 mmHg. The patient was placed in a semi-recumbent position and the adverse event resolved in 1 hour. The adverse event was judged by the Investigator as mild in severity and unlikely related to the study drug. The same subject experienced another episode of orthostatic hypotension after receiving Treatment C. (Naloxone HCL IV injection). The baseline vital signs before getting the study drug were BP 119/67 mmHg and 68 and BP 103/63, HR 58 one hour after the study drug exposure. The adverse event was treated with a cold pack and resolved in approximately 15 minutes. The adverse event was judged by the Investigator as mild in severity and possibly related to the study drug.

Subject (b) (6)**,** is a 37-year-old, white Hispanic female who had a history of elective rhinoplasty and no concomitant medications. Approximately four days after receiving Treatment A (Naloxone nasal spray 8 mg, 20%) the subject experienced vasovagal symptoms that resolved 4 minutes later without any action taken. The adverse event was judged by the Investigator as mild in severity and unlikely to be related to the study drug.

Subject (b) (6), a 20-year-old black male with no significant medical history was reported to have neutropenia approximately 1 day after getting Treatment B (Naloxone nasal spray, 8 mg (b) (4)%).

At the screening, on (b) (6) the absolute neutrophil count was 2.1 x 10^9/L (normal range

1.5-6.1 x 10^9/L) and the neutrophil/leukocyte was 40% (normal range 34-71%). On (b) (6) the absolute neutrophil count was 0.8 x 10^9/L and the neutrophil/leukocyte was 24%. No action was taken to treat the adverse event. The subject failed to return to the clinic for additional tests.

Reviewer comment: The orthostatic hypotension is likely a consequence of a study procedure and unrelated to Naloxone. I agree with the Applicant's conclusions that the orthostatic hypotension is not related to the study drug in both cases (Subject (b) (6) and Subject (b) (6)). In addition, one of the patients experienced a second event of orthostatic hypotension after IV administration of Naloxone and not to the proposed intranasal study drug.

Subject (b) (6) in study group of naloxone nasal spray 8 mg, (b) (4)% alcohol, experienced neutropenia with a significant drop in neutrophil count: absolute neutrophil count was 2.1 x 10^9/L (normal range 1.5-6.1 x 10^9/L) on April 2, 2018 and went down to 0.8 x 10^9/L on May 6, 2018. The Applicant reported that no additional information is available because the subject did not return for a follow up visit. There is insufficient information to make any clear conclusion on neutropenia and its clinical relevance. It is important to note, that the adverse event was observed after use of 8 mg nasal Naloxone containing (b) (4)% of alcohol and not the formulation intended to be marketed. The Applicant listed adverse events as significant that did not appear to match the definition articulated in the Agency guidance. These adverse events do not change the risk-benefit assessment for the product.

9.4.5. Treatment Emergent Adverse Events and Adverse Reactions/L

The total number of TEAEs in the pooled studies were 65 reported by 21 (43.8%) subjects following dose administration in the Naloxone nasal spray studies. All adverse events were mild and moderate in severity. There was no study discontinuation due to the adverse events Twenty-one AEs were reported by 12 (25.5%) subjects receiving Naloxone nasal spray 8 mg, containing 20% alcohol from both PK studies. Of these, two subjects reported nasal discomfort and eight AEs (dizziness reported by two subjects, asthenia, palpitations, dry mouth, headache, somnolence, and tremor reported once per subject).

Fifteen AEs were reported by 10 (20.8%) subjects in Naloxone nasal spray 8 mg, containing (b) (4)% alcohol. One AE (dizziness), three AEs (vomiting, nausea, and headache), four AEs (dizziness, somnolence, and diarrhea

The most common TEAEs by System Organ Class from the pooled studies occurred in the following SOCs:

- Nervous system disorders (22.9%)
- Gastrointestinal disorder (18.8%)
- General disorders and administration site conditions (8.3%)

Summary of treatment emergent adverse events for the pooled datasets, Studies INS012-17-108 and INS012-18-119 are presented in the Table 10.

Table 10: Treatment Emergent Adverse Events by MedDRA SOC and PT in the Pooled Datasets, Studies INS012-17-108 and INS012-18-119

MedDRA Primary System Organ Class MedDRA Preferred Term	Statistic	Naloxone Nasal Spray, 8 mg (20% alcohol) (N=47)	Naloxone Nasal Spray, 8 mg (b)(4) alcohol) (N=48)	Naloxone HCL IM Injection, 0.4 mg/mL (N=47)	Naloxone HCL IV Injection, 2 mg (1 mg/mL) (N=24)	Overall (N=48)
Nervous system disorders	N (%)	6 (12.8)	5 (10.4)	3 (6.4)	6 (25.0)	11 (22.9)
Dizziness	N (%)	2 (4.3)	2 (4.2)	2 (4.3)	5 (20.8)	7 (14.6)
Headache	N (%)	2 (4.3)	2 (4.2)	2 (4.3)	1 (4.2)	4 (8.3)
Presyncope	N (%)	2 (4.3)	0	0	1 (4.2)	2 (4.2)
Somnolence	N (%)	1 (2.1)	1 (2.1)	0	0	1 (2.1)
Tremor	N (%)	1 (2.1)	0	0	0	1 (2.1)
Gastrointestinal disorders	N (%)	4 (8.5)	3 (6.3)	1 (2.1)	3 (12.5)	9 (18.8)
Nausea	N (%)	1 (2.1)	1 (2.1)	1 (2.1)	0	3 (6.3)
Abdominal pain	N (%)	2 (4.3)	0	0	0	2 (4.2)
Diarrhea	N (%)	0	1 (2.1)	1 (2.1)	0	2 (4.2)
Dry mouth	N (%)	1 (2.1)	0	1 (2.1)	0	2 (4.2)
Dyspepsia	N (%)	0	0	1 (2.1)	1 (4.2)	2 (4.2)
Abdominal discomfort	N (%)	0	1 (2.1)	0	0	1 (2.1)
Aphthous ulcer	N (%)	0	0	0	1 (4.2)	1 (2.1)
Dental discomfort	N (%)	0	0	0	1 (4.2)	1 (2.1)
Salivary hypersecretion	N (%)	1 (2.1)	0	0	0	1 (2.1)
Toothache	N (%)	0	0	0	1 (4.2)	1 (2.1)
Vomiting	N (%)	0	1 (2.1)	0	0	1 (2.1)
General disorders and administration site conditions	N (%)	2 (4.3)	0	2 (4.3)	1 (4.2)	4 (8.3)
Asthenia	N (%)	2 (4.3)	0	0	0	2 (4.2)
Fatigue	N (%)	0	0	1 (2.1)	1 (4.2)	2 (4.2)
Vessel puncture site pain	N (%)	0	0	1 (2.1)	0	1 (2.1)
Respiratory, thoracic and mediastinal disorders	N (%)	2 (4.3)	0	2 (4.3)	1 (4.2)	4 (8.3)
Nasal congestion	N (%)	0	0	2 (4.3)	1 (4.2)	2 (4.2)
Nasal discomfort	N (%)	2 (4.3)	0	0	0	2 (4.2)
Eye disorders	N (%)	1 (2.1)	0	0	1 (4.2)	2 (4.2)
Conjunctival hyperemia	N (%)	1 (2.1)	0	0	0	1 (2.1)
Vision blurred	N (%)	0	0	0	1 (4.2)	1 (2.1)

MedDRA Primary System Organ Class MedDRA Preferred Term	Statistic	Naloxone Nasal Spray, 8 mg (20% alcohol) (N=47)	Naloxone Nasal Spray, 8 mg (b)% alcohol) (N=48)	Naloxone HCL IM Injection, 0.4 mg/mL (N=47)	Naloxone HCL IV Injection, 2 mg (1 mg/mL) (N=24)	Overall (N=48)
Musculoskeletal and connective tissue disorders	N (%)	1 (2.1)	1 (2.1)	0	0	2 (4.2)
Back pain	N (%)	0	1 (2.1)	0	0	1 (2.1)
Musculoskeletal chest pain	N (%)	1 (2.1)	0	0	0	1 (2.1)
Vascular disorders	N (%)	1 (2.1)	1 (2.1)	0	0	2 (4.2)
Flushing	N (%)	0	1 (2.1)	0	0	1 (2.1)
Orthostatic hypotension	N (%)	1 (2.1)	0	0	0	1 (2.1)
Blood and lymphatic system disorders	N (%)	0	1 (2.1)	0	0	1 (2.1)
Neutropenia	N (%)	0	1 (2.1)	0	0	1 (2.1)
Cardiac disorders	N (%)	1 (2.1)	0	0	0	1 (2.1)
Palpitations	N (%)	1 (2.1)	0	0	0	1 (2.1)
Ear and labyrinth disorders	N (%)	0	1 (2.1)	0	0	1 (2.1)
Hypoacusis	N (%)	0	1 (2.1)	0	0	1 (2.1)
Injury, poisoning and procedural complications	N (%)	0	0	0	1 (4.2)	1 (2.1)
Tooth fracture	N (%)	0	0	0	1 (4.2)	1 (2.1)
Psychiatric disorders	N (%)	0	0	1 (2.1)	0	1 (2.1)
Distractibility	N (%)	0	0	1 (2.1)	0	1 (2.1)
Renal and urinary disorders	N (%)	0	1 (2.1)	0	0	1 (2.1)
Urine odor abnormal	N (%)	0	1 (2.1)	0	0	1 (2.1)
Skin and subcutaneous tissue disorders	N (%)	0	1 (2.1)	0	0	1 (2.1)
Dermatitis	N (%)	0	1 (2.1)	0	0	1 (2.1)

N = number of subjects; Subjects were only counted once within each preferred term and treatment group, and once within the overall summary.

Source: Summary of clinical safety, table 13.

Reviewer comment: The only adverse events reported twice after introduction of 8 mg nasal Naloxone with 20% of alcohol by were dizziness, headache, presyncope, asthenia, and nasal discomfort. Overall, there are no new safety signals for 8 mg nasal Naloxone containing 20% alcohol or new findings that could alter the risk-benefit profile of Naloxone. I verified the adverse events summaries presented by the Sponsor by reviewing ISS datasets for individual studies. There were no new safety findings that will alter the known risk-benefit profile of Naloxone.

Table 11: Treatment Emergent Adverse Events by MedDRA PT and Time of Onset-Pooled Datasets

MedDRA Primary SOC MEDDRA Preferred Term	Time of Onset	Naloxone Nasal Spray 8 mg (20% alcohol) N=47 N (%)
Nervous system		
Dizziness	0-1 day	2 (4.3)
Headache	0-1 day	1 (2.1)
	≥ 2 days to ≤ 7 days	1 (2.1)
	0-1 day	1 (2.1)
	≥ 2 days to ≤ 7 days	1 (2.1)
Somnolence	0-1 day	1 (2.1)
Tremor	0-1 day	1 (2.1)
Gastrointestinal disorders		
Nausea	0-1 day	1 (2.1)
Abdominal pain	0-1 day	1 (2.1)
	≥ 2 days to ≤ 7 days	1 (2.1)
Dry mouth	0-1 day	1 (2.1)
Salivary hypersecretion	0-1 day	1 (2.1)
General disorders and administration site conditions		
Asthenia	0-1 day	1 (2.1)
	≥ 2 days to ≤ 7 days	1 (2.1)
Respiratory, thoracic and mediastinal disorder		
Nasal discomfort	0-1 day	1 (2.1)
	≥ 2 days to ≤ 7 days	1 (2.1)
Eye disorders		
Conjunctival hyperemia	≥ 2 days to ≤ 7 days	1 (2.1)
Musculoskeletal and connective tissue disorders		
Musculoskeletal chest pain	≥ 2 days to ≤ 7 days	1 (2.1)
Vascular disorders		
Orthostatic hypotension	0-1 day	1 (2.1)
Cardiac disorders		
Palpitations	0-1 day	1 (2.1)

Source: Created by the reviewer based on Table 4-8 of Naloxone nasal spray submission
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class

Reviewer comment: Overall, there are no newly identified safety signals. All adverse events were mild in severity and didn't require intervention or study discontinuation. I reviewed the Applicant's datasets and found no substantial differences that would affect my perception of the adverse event profile.

Nasal cavity examination and irritation test results:

Study INS012-17-108. Of 24 subjects in the study, one subject had two nasal cavity irritation findings observed during the Period 3 examination (30 minutes and 1-hour

after the dose) after treatment with 8 mg Naloxone nasal spray with (b)(4)% alcohol. Both times the findings were not clinically significant scores of 1 (i.e., inflamed mucosa, no bleeding) in the right nostril. On 4-hour and 24-hour examinations after dosing, there were no signs of nasal cavity irritation.
Study INS012-18-119. Of 24 subjects in the study, five subjects had nasal cavity irritation in the Naloxone nasal spray 8 mg (20% alcohol) group. Of these, four subjects had scores of 1 (inflamed mucosa, no bleeding) and one had a score of 2 (minor bleeding that stopped within one minute). All five subjects had no nasal irritation at the end of the study. Roughly 30% (7 out of 24) of subjects had nasal irritation after getting the 8 mg Naloxone nasal spray containing 20% of alcohol.
Seven subjects had nasal irritation in the Naloxone nasal spray 8 mg (b)(4)% alcohol) group and had a score of 1. Mild erythema was reported for two subjects. All seven subjects had no nasal irritation at the end of the study.
The Applicant concluded that of 12 subjects who had nasal irritation, 11 were not clinically significant (subject had score 1, i.e. inflamed mucosa, no bleeding) and one subject with score 2 (i.e. minor bleeding which stopped within 1 minute).

Reviewer comment: The majority of subjects had no nasal irritation. Erosions were not observed in any subjects. All subjects except for one were scored no higher than "1" and one subject had minor bleeding that resolved within a minute with no intervention. There was only one subject who scored "2" and had a minor bleeding after 8 mg nasal naloxone with 20% of alcohol that resolved within a minute. I reviewed the nasal irritation test results and calculated 7 subject who reported nasal irritation after 8 mg nasal naloxone with 20% of alcohol rather than 5 subjects presented by the Applicant. The discrepancies were minor and did not impact the safety conclusion. The nasal irritation assessment tool and monitoring are adequate to evaluate the potential for local toxicity. The risk is acceptable given the potentially life-saving benefits of this medication. The potential for local irritation will be communicated in labeling.

Olfactory test results:

In Study INS012-17-108 after reviewing data in olfactory function tests, I identified 3 subjects who scored 8 on 1-12 olfactory testing scale. Of these three subjects, two (Subjects (b)(6)) had abnormal (low) (8) olfactory test results during the study, and test results went back to normal on the last day (Day 10) tested.
• Subject (b)(6) had a score of 9 at the screening and went down to 7 on Day 1 before getting the study drug. The test score was 8 on Day 2, 24 hours after receiving Treatment A (Naloxone nasal 8 mg 20% alcohol) and on Day 9 before getting the Treatment B (Naloxone nasal 8 mg (b)(4)% alcohol). Test results went back to normal on

Day 10 24 hours after getting Treatment B (Naloxone nasal 8 mg (b)(4)% alcohol).
• Subject (b)(6) had a score of 8 before getting treatment C (Naloxone HCL IM injection, 0.4 mg/mL) on Day 1, the score went up to 10 on Day 5 and remained normal through Day 10.
• Subject (b)(6) scored 9 on olfactory function testing at the screening and the score remained in the normal range until Day 9. The score dropped to 8 on Day 9 and Day 10. The score for the olfactory function test remained 8 on Day 10 24 hours after Treatment B (Naloxone nasal 8 mg (b)(4)% alcohol).

In the Study INS012-18-119 there were no treatment-emergent abnormal olfactory function test results identified.
I identified one subject who reported to have transient low olfactory test result before the study drug was introduced.
• Subject (b)(6), had a normal olfactory test result at the screening (score=10), then score went down to 8 on Day 1 before getting the Treatment B (Naloxone nasal 8 mg (b)(4)% alcohol). The score went back to normal (10) on Day 2, 24-hour after getting Treatment B (Naloxone nasal 8 mg (b)(4)% alcohol) and stayed within the normal range on Days 13 and 14 (scored 10, 10, and 11).

Reviewer comment: Results of olfactory test results demonstrated that some subjects experienced a transient slight decrease of olfactory test results. In addition, there was only one subject who had a new abnormal olfactory test results after the introduction of the study drug and the abnormal results was after receiving the (b)(4)% alcohol formulation, not the 20% alcohol formulation that is proposed for marketing. Olfactory test results do not raise any significant safety concerns.

9.4.6. Laboratory Findings

9.4.7. Vital Signs

Vital signs assessment consisted of seated systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature at screening, prior to dosing, and at the end of the study or early withdrawal at approximately 1, 2, and 24 hours after dosing. There were no clinically significant changes from baseline in any of the vital signs during the pooled studies.
I verified the Applicant's analysis by examining the Integrated Summary (ISS) datasets.

Reviewer comment: In both pivotal studies, no clinically significant findings were noted for any chemistry, hematology, or urinalysis results in any groups. I reviewed the data tables provided by the Applicant and did not identify any clinically relevant laboratory findings. My review of the vital signs data for the pooled studies confirmed the conclusions made by the Applicant and did not raise any safety concerns.

9.4.8. Electrocardiograms (ECGs)

Not applicable

9.4.9. QT

Not applicable

9.4.10. Immunogenicity

Not applicable

9.5. Analysis of Submission-Specific Safety Issues

9.5.1. [Name Safety Issue]

Naloxone has been used for many years and has a relatively favorable risk/benefit profile. In particular, naloxone has been administered safely at high doses to patients who are not opioid-dependent. However, use of Naloxone may precipitate opioid withdrawal in patients who are opioid dependent. Opioid withdrawal is characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. The severity and duration of the withdrawal syndrome are known to be related to the dose of Naloxone and to the degree and type of opioid dependence. Withdrawal symptoms may appear within minutes of administration and subside in about 2 hours. In neonates, opioid withdrawal may be life-threatening. Risk of precipitation of opioid withdrawal is increasing with use of higher dose of Naloxone. Since the proposed dose of Naloxone is 8 mg, there may be a higher risk for precipitation of opioid withdrawal symptoms in opioid-dependent patients compared to naloxone products that produce lower exposures.

9.6. Safety Analyses by Demographic Subgroups

Not applicable

9.7. Specific Safety Studies/Clinical Trials

No additional safety studies or updates were submitted for review.

9.8. Additional Safety Explorations

9.8.1. Human Carcinogenicity or Tumor Development

Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed

9.8.2. Human Reproduction and Pregnancy

There were no reports of pregnancy in Study INS012-17-108 and Study INS012-18-119 or pooled studies.

9.8.3. Pediatrics and Assessment of Effects on Growth

No pediatric clinical studies are proposed, because pharmacokinetics studies in healthy, pediatric patients would involve more than minimal risk without the prospect of direct benefit to the population. Furthermore, PK studies cannot be conducted in a pediatric opioid overdose population, because it is immediately life- threatening condition and PK samples cannot be collected in the context or emergency treatment of the overdose, in addition to other ethical considerations that preclude conducting studies.
The Sponsor submitted an Agreed Pediatric Study Plan on April 30, 2019. The pediatric plan relies upon the safety and effectiveness of Naloxone injection products in the post-marketing setting as well as data available in the medical literature, and clinical practice guidance.
The division of Pediatric and Maternal Health (DPMH) have been consulted to assist in the review of the submitted pediatric information, label, and approval recommendations including the Pregnancy and Lactation Rule (PLLR) language. The Pediatric and Maternal Health consults are pending at this time.

Refer to section 8.1 for more details on pediatric assessment of efficacy.

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

There is no clinical experience with naloxone HCL with regard to overdose in humans. Naloxone does not have any known abuse potential since it does not produce subjective effects or physical dependence and precipitates abstinence in morphine-dependent subjects. There is no available data regarding withdrawal and rebound in humans.

9.9. Safety in the Postmarket Setting

9.9.1. Safety Concerns Identified Through Postmarket Experience

Naloxone has been widely marketed in the United States for over than 40 years with a well-known safety profile. The safety of Naloxone has been under regular review through postmarketing studies. Based on the available data from spontaneous reporting and literature

review, the benefit-risk assessment of Naloxone remains unchanged.

9.9.2. Expectations on Safety in the Postmarket Setting

No postmarketing requirements are recommended at this time.

9.9.3. Additional Safety Issues From Other Disciplines

9.10. Integrated Assessment of Safety

Review of the safety data from studies INS012-17-108 and INS012-18-119 revealed no new safety signals with use of 8 mf nasal naloxone containing 20% of alcohol. The most common adverse reactions from 8 mg nasal naloxone with 20% of alcohol that were reported twice (4.3%) are dizziness, headache, presyncope, abdominal pain, asthenia, and nasal discomfort. Review of local toxicity on nasal cavity and olfactory nerve did not raise any safety concerns.

The Applicant conducted a literature review which was presented with the NDA submission to support the safety and efficacy of 8 mg Naloxone. Naloxone is the standard of care with no absolute contraindications for the treatment of opioid-related respiratory depression regardless of age, sex, or ethnicity. Cardiovascular events, pulmonary edema, and seizures have been reported in the presented literature. However, separating the effects of naloxone from the effects of concomitant medications and pre-existing disorders have been problematic. Overall, naloxone is considered to have a wide safety margin. Analysis of the literature with use of naloxone in doses much higher than 8 mg did not reveal any adverse events that raise concerns about safety and effectiveness of naloxone for the treatment of respiratory depression secondary to opioid overdose. After review of the literature submitted and my own review of PubMed database, I concluded that analysis of the literature supports the safety and effectiveness of high dose naloxone for the treatment of respiratory depression secondary to opioid overdose.

The main risk of naloxone in the setting of reversing opioid overdose is severe opioid withdrawal in those physically dependent on opioids. This risk is likely associated with Cmax. Given that the Cmax of naloxone for this product was lower compared to the reference product 2 mg IV dose, it is anticipated that 8 mg Naloxone will have a risk of causing severe opioid withdrawal that is comparable to the reference product when the reference product is dosed at the upper end of the approved dose range in both single and multiple dose administrations.

10. Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting held for this drug product.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Office of Prescription Drug Promotion (OPDP) and The Division of Medication Error Prevention and Analysis (DMEPA) have not agreed to the proposed product names.
Additionally, the Division of Pediatric and Maternal Health (DPMH) was consulted regarding the proposed labeling (i.e., pregnancy and lactation labeling rule, PLLR). DPMH provided recommendations for the proposed labeling, based on their review.
Labeling is ongoing at the time of this writing, and specific recommendations have been made in the relevant sections of this review.
Based on the discussion with other disciplines I recommend the following changes to the prescription information:
I. Update the non-product specific language in sections 2. Dosage and administration, section 5.1. Warning and precautions, 5.2. Risk of recurrent respiratory and central nervous system depression to be consistent with recently approved naloxone products
II. Revise the wording and to accurately describe adverse events after abrupt reversal of an opioid overdose.
III. Revise the highlights of the labeling to comply with the FDA's Prescription Drug Labeling recommendations.

11.2. Nonprescription Drug Labeling

Not applicable.

12. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not recommended at this time.

13. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended at this time.

14. Appendices

14.1. References

14.2. 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 with clinical investigators were made which could affect the outcome of effect the outcome of the studies as defined in 21 CFR 54.2(a) and no listed investigators were the recipients of significant payments of other sort as defined in 21 CFR 54.2(f).

Covered Clinical Study (Name and/or Number): INS012-17-108 and INS012-18-119

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 8		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): Note identified		

<table>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Note identified</td></tr>
<tr><td colspan="3">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

Sponsor of covered study: _____</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☐</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☐</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☐</td><td>No ☐ (Request explanation from Applicant)</td></tr>
</table>

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/

IZABELLA KHACHIKYAN
01/29/2020 02:22:39 PM

PAMELA J HORN
01/29/2020 02:55:01 PM
I concur with the conclusions described in the clinical review