Cross-Discipline Team Leader Review

Date	2/6/2020
From	Pamela Horn, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	212045
Applicant	Hikma Pharmaceuticals USA, Inc
Date of Submission	April 30, 2019
PDUFA Goal Date	February 28, 2020
Proprietary Name	
Established or Proper Name	Naloxone HCl
Dosage Form(s)	Nasal spray
Applicant Proposed Indication(s)/Population(s)	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/ or central nervous system depression for adult and pediatric patients
Applicant Proposed Dosing Regimen(s)	One 8 mg spray into one nostril
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	
Recommended Dosing Regimen(s) (if applicable)	

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Naloxone is a nonselective opioid receptor antagonist with the greatest affinity for the mu-opioid receptor. It is used to reverse life-threatening opioid overdose and prevent hypoxia associated with injury and death.

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 patients and 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. Narcan nasal spray (naloxone hydrochloride; NDA 208411) was approved on November 18, 2015 and is approved in a single-dose 2 mg and 4 mg strength.

As more potent and faster onset synthetic opioids have been implicated in opioid overdose deaths in recent years, it has been hypothesized that larger doses of antagonist may be necessary than are available in currently approved single-dose devices to reverse the opioid overdose. The Applicant's rationale for developing this 8 mg naloxone nasal spray is to make a product available for community use that delivers higher exposures than other products approved for community use. The Applicant has not provided comparative efficacy, safety or pharmacokinetic data to the aforementioned products approved for community use to inform the potential role of this product in the existing armamentarium for treating opioid overdose.

The efficacy of the proposed product is supported by a scientific bridge between the proposed product and the reference product, Narcan, 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 high potency 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 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 the pharmacokinetic studies in healthy volunteers were dizziness, headache, presyncope, abdominal pain, asthenia, and nasal discomfort. The safety profile is acceptable.

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.

However, due to CMC and device deficiencies, including lack of human factors data to demonstrate that the final finished combination product user interface would maximize the likelihood that the product will be safely and effectively used by intended users, a complete response is recommended.

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 • Recent rates of increase in opioid overdose cases are highest for high potency synthetic opioids such as fentanyl and carfentanil	Opioid overdose is a serious life-threatening condition that contributes to a significant number of deaths.
Current Treatment Options	• There are multiple drugs currently approved by FDA for the treatment of opioid overdose • The duration of antagonists such as naloxone are generally shorter than the duration of action of most opioids • Multiple naloxone administrations are sometimes required with high potency synthetic opioids	There are FDA-approved treatment options for opioid overdose. There may be a role for products with a higher dose or longer duration of action Wide availability of high potency synthetic 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
Benefit	• The efficacy of this 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. • The efficacy of this product in the entire pediatric age range is supported by literature • There are no clinical efficacy data for this product to assess its efficacy in treating overdoses from high potency synthetic opioids • There are no comparative efficacy data between this product and other	The available data provide substantial evidence to support the effectiveness of naloxone nasal spray for the target adult and pediatric population. The pharmacokinetic data do not raise concern that this product would result in delayed or inadequate exposure compared to other approved naloxone products The application contains no evidence that this product will result in improved outcomes in reversing synthetic opioids compared to available

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	approved naloxone products	products
Risk and Risk Management	• The most frequent adverse events with the 20% alcohol containing formulation from two PK trials were dizziness, headache, abdominal pain, presyncope, and nasal discomfort. • All adverse events were mild to moderate in severity. • Nasal and olfactory tests results do not raise any clinically significant safety concerns. • There were no deaths or serious adverse events • There is literature support for the safety of the use doses exceeding the proposed dose for this product in adults and in the entire pediatric age range • There are nonclinical toxicology data to support the safety of the 20% alcohol formulation in pediatric patients • 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 in adults • An association between pulmonary complications and higher naloxone doses has been reported in a recent publication • Proposed product labeling includes prominent language about the serious risks of precipitating acute opioid withdrawal in the neonate to mitigate the risk of precipitated withdrawal in this population. • There are no comparative safety data between this product and other naloxone products to inform prescribing decisions when choosing a product for opioid reversal	There are no clinically significant safety concerns with use of 8 mg Naloxone containing 20% of alcohol for the proposed indication. No additional safety information is needed in the postmarket setting and no postmarketing requirements are recommended. Routine pharmacovigilance is adequate to assess the postmarket safety experience, including the potential for this product to precipitate acute opioid withdrawal in opioid-dependent individuals. Additional measures to mitigate risk beyond the information provided in the labeling are not warranted.

2. Background

Hikma is the current Applicant for this new drug application (NDA) for naloxone HCl nasal spray submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/ or central nervous system depression for adult and pediatric patients. The nasal spray is a single-use, drug-device combination product proposed intended for use in the community. Two sprays are proposed to be included in each package. It is designed for use in non-healthcare settings by laypersons to rescue patients experiencing life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention. The Applicant conducted the clinical development program under INDs 126173 and 134954. Application ownership was transferred from Insys to Hikma after NDA submission.

The Applicant submitted bioavailability data to reference Narcan (naloxone HCl; NDA 16636), an injectable formulation of naloxone. Narcan was approved April 13, 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, including propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine. 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). Therefore, the Applicant used a generic naloxone product in the pivotal relative bioavailability study to create a scientific bridge to their NDA for Narcan to establish the safety and efficacy of naloxone nasal spray for the proposed indication. In addition, this NDA is relying on the published literature to support the safety of the product in adults and the safety and efficacy of the product in the pediatric population.

The following differences between naloxone nasal spray and Narcan must be addressed in the evaluation of this application.

1. Naloxone nasal spray represents a change in the route of administration from intravenous (IV), intramuscular (IM), or subcutaneous (SC) injection to intranasal (IN). The intranasal route of administration differs in its pharmacokinetic profile compared to the approved parenteral routes. It is therefore important to confirm that naloxone nasal spray achieves comparable or greater systemic exposures to naloxone as compared to Narcan, particularly in the period immediately after drug administration, as this represents a critical period in which the patient's opioid overdose must be reversed to avoid irreversible injury or death
2. This new formulation is intended to come in contact with the nasal mucosa and the formulation contains ethanol. Therefore, the Applicant evaluated the potential for local toxicity in the relative bioavailability studies.
3. Narcan nasal spray represents a change in the intended use setting. Narcan is generally used in healthcare settings by healthcare professionals, whereas naloxone nasal spray is intended to be used in a community setting by laypersons. The Applicant was advised

during development that a human factors evaluation to support use in this different setting is required for product approval.

4. Lastly, there are issues regarding the use in pediatric patients. The proposed dosing for naloxone nasal spray is a fixed dose while Narcan labeling recommends weight-based dosing in pediatric patients. In addition, the presence of alcohol in the formulation necessitated a nonclinical juvenile toxicity assessment.

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5. Product Quality

There are unresolved product quality issues that preclude approval. The Product Quality review was conducted by Dr. Sam Bain, Dr. Donna Christner, Dr. Jizhou Wang, Dr. Julia Pinto, Yeung Chan, Yaodong (Tony) Huang, Dr. Julia Marre, and Denise Miller. Portions of the summary below are excerpted from the Integrated Quality Assessment.

- *General product quality considerations:*
  Drug Substance: USP has a monograph for the drug substance, Naloxone Hydrochloride. For the drug substance CMC, the Applicant has referenced DMF (b) (4), which has been found adequate by the Agency. The NDA includes the Applicant's controls of the drug substance, which include compliance with USP monograph and ICH guidelines, and critical aspects of the DMF holder's specification. Based upon the current adequacy of the DMF and the information provided in the NDA, the drug substance manufacturing process, characterization, shelf-life specification, container closure system and stability are satisfactory.

  Drug Product: Naloxone Nasal Spray finished drug product is a nasal spray formulation supplied in a unit dose nasal spray container. The spray device delivers about 100 µL of Naloxone Nasal Spray, in turn delivering 8 mg of Naloxone Hydrochloride per spray. There were multiple deficiencies identified in the drug product review. Significant fluctuation for edetate disodium dihydrate (EDTA) across different timepoints and different batches was identified. The Applicant has committed to investigate the root reasons for the variation and re-validate the analytic methods. However, the planned date to provide the required information is August 2020. Issues in the extractables studies included discrepancies in calculation of maximum daily doses and missing information about an extract. Issues in the leachable studies included inadequate study design elements, unacceptable and missing acceptance criteria, deficiencies in the analytical methods and incomplete documentation of method validation.

  Manufacturing: The drug product manufacturing (b) (4) (b) (4) (b) (4) The following deficiencies were identified during the review: No scale up has been proposed, (b) (4) (b) (4), IPC specifications for pH, viscosity, and density were

not provided, (b) (4) and extractable and leachable risks (b) (4) have not been sufficiently addressed.

Microbiology: This is a non-sterile, aqueous, non-preserved, single-use, nasal spray drug product; packaged in a unit-dose spray device that delivers the entire contents of the drug product in one spray (single-use). The Applicant provided adequate information to support the self-preserving nature, the routine release testing, and the stability testing of the drug product. The applicant has not manufactured exhibit batches at the newly proposed, Hikma Columbus, Ohio site and, therefore, there are no executed batch records for this new facility. It is expected that the Applicant will provide these documents in the future, as part of a resubmission.

- *Facilities review/inspection:* The drug substance manufacturing facility has experience manufacturing the API and is currently cGMP compliant and is deemed approvable at this time. Given this is a high-risk drug-device combo product and site transfer activities include transport of equipment, IQ/OQ/PQ of manufacturing line, and production of 3 new exhibit batches, a PAI was requested by OPMA and CDRH reviewers. However, as the new facility will not be ready for the inspection until June 30, 2020, a complete response has been recommended by OPMA/OPQ and CDRH reviewers

- *Other notable issues (resolved or outstanding)*:

The submission did not include adequate information on the device constituent parts of the combination product, which is a nasal spray device.
The following image of the device is from p. 6 of the review:

The nasal spray is designed to deliver a single dose without priming and cannot be reused. The review covered the following topics: labeling, design control summary, risk analysis, design verification, and facilities and quality systems. Human factors validation was discussed in the review, but the final recommendations were deferred to the CDER/DMEPA review team. The review team recommends a complete response due to the following deficiencies:

1. Additional information about the CAPA procedure is required to assess its adequacy.
2. There are several outstanding information requests. The Sponsor plans to respond at the end of June 2020, after the PDUFA goal date. See the CDRH review for details.

Insufficient information was provided to support a human factors review during the review cycle. The Division of Medication Error Prevention and Analysis (DMEPA) noted in their labeling review that the results of the HF validation study were not submitted and that the current Applicant has given an estimated submission date for these results of March 2020.

6. Nonclinical Pharmacology/Toxicology

The final nonclinical review is pending.

The preliminary conclusions of the nonclinical review with respect to the juvenile rat study are relevant to the benefit-risk profile of the product in neonates and are summarized here. The to-be-marketed product contains 20% ethanol and (b) (4) propylene glycol. The total amount per dose for ethanol and propylene glycol does not exceed recommended daily limits for pediatric patients, except for the amount of ethanol in neonates (i.e., (b) (4) mg per spray) for which a safe limit has not been identified. Therefore, in accordance with Agency guidance, the applicant conducted a juvenile animal study in rats with a human equivalent age of a preterm neonate to identify a NOAEL of naloxone and excipients and to fully characterize the potential local and systemic toxicity of these components in pediatric patients, particularly with respect to ethanol and propylene exposure and the effects on the CNS. The juvenile rat study dosed rat pups with 0, 1.6, 2.4, or 3.2 mg/day naloxone using 2 concentrations of alcohol (20% and (b) (4)%) in combination with (b) (4) propylene glycol as well as a saline control intranasally in divided doses, one per nostril as a single daily dose with a 28-day recovery period. All groups were examined for neurohistopathology, sexual maturity, social behavior, and learning and memory at appropriate timepoints and there were no effects from intranasal administration of naloxone or excipients on any of these endpoints.

7. Clinical Pharmacology

The Clinical Pharmacology review was conducted by Dr. Wei Qui and Dr. Yun Xu. The application has been found acceptable from the clinical pharmacology perspective.

The following key findings are excerpted from Dr. Qui's review.

1. In two comparative bioavailability studies, a single dose of Naloxone Nasal Spray 8 mg containing 20% alcohol (the final to-be-marketed formulation) exhibits comparable median Tmax (15 min), greater unconjugated naloxone concentrations at all time points including earlier time points (i.e., 2, 4, 6, 8, 10 min post-dose), 14-fold greater Cmax and 10-fold greater AUClast or AUC0-inf values than a single dose of 0.4 mg intramuscular (IM) injection, which is within the approved initial dose range (i.e., 0.4 to 2 mg) for the listed drug Narcan Injectable. The relative bioavailability of Naloxone Nasal Spray 8 mg containing 20% alcohol is 41.6 – 47.4% in comparison to an IM injection based on dose normalized exposure.
2. A single dose of Naloxone Nasal Spray 8 mg containing 20% alcohol exhibits an unconjugated naloxone Cmax value of 12.8 ng/mL, which is lower than the unconjugated naloxone concentration at 2 min post-dose (26.2 ng/mL) for a single dose of the listed drug Narcan Injectable at 2 mg IV injection. The corresponding AUClast and AUC0-inf values for Naloxone Nasal Spray 8 mg containing 20% alcohol are 42% and 48% greater than the 2 mg IV injection, respectively. The absolute bioavailability is 36.6% for the Naloxone Nasal Spray 8 mg containing 20% alcohol in comparison to an IV injection based on dose normalized exposure.

The observation that greater naloxone concentrations were observed at the early time points addresses the requirement that naloxone nasal spray achieves comparable or greater systemic exposures to naloxone as compared to Narcan in the period immediately after drug administration, as this represents a critical period in which the patient's opioid overdose must be reversed.

These early time points are included in figure 1 of the review:

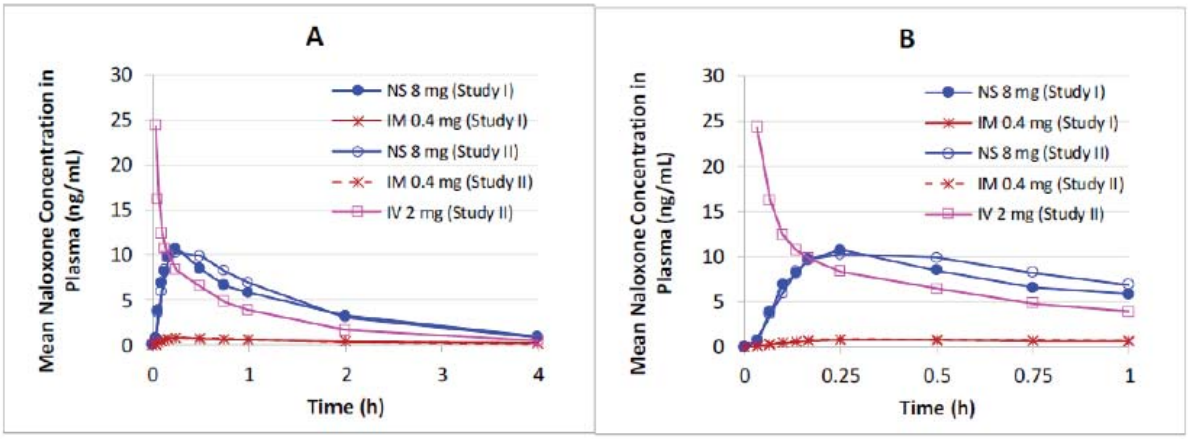

Figure 1 Mean Plasma Concentration Profiles of Unconjugated Naloxone Following a Single Dose of Naloxone Nasal Spray 8 mg Containing 20% Alcohol (NS 8 mg) versus 0.4 mg IM Injection (IM 0.4 mg) and 2 mg IV Injection (IV 2 mg) in Healthy Subjects
(Panel A: 0 – 4 h and Panel B: 0 – 1 h) (Studies INS012-17-108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

The observation that the AUC values are higher for naloxone nasal spray than the reference naloxone 2 mg IV is also depicted in figure 1. The pharmacokinetic study data provide an adequate scientific bridge to rely on the Agency's previous finding of efficacy. However, while the Cmax data support reliance on the previous finding of safety, due to the higher AUC

values compared to the reference product, the data do not provide a scientific bridge to the previous Agency finding of safety for Narcan. See the section on clinical safety for a discussion of literature support for the safety of the proposed product.

8. Clinical Microbiology

Not applicable

9. Clinical/Statistical- Efficacy

The clinical review was conducted by Dr. Izabella Khachikyan. No new clinical efficacy studies were submitted in support of this application. The Applicant is referencing the NDA for Narcan (naloxone hydrochloride, NDA 16636), which is approved for known or suspected opioid overdose, to establish the efficacy of the proposed product.

10. Safety

Safety data were generated in 48 health adult volunteers from two clinical pharmacology studies, INS012-17-108 and INS012-18-119, using the to-be-marketed formulation. These studies included routine clinical safety assessments as well as local assessments of the nasal cavity and olfactory nerve function. See Dr. Khachikyan's review for details of the study design and safety assessments. Review of the safety data from pharmacokinetic studies INS012-17-108 and INS012-18-119 revealed no new safety signals with use of 8 mg nasal naloxone containing 20% of alcohol. There were no deaths or serious adverse events in the healthy volunteers exposed to the investigational product. Common adverse reactions were dizziness, headache, presyncope, abdominal pain, asthenia, and nasal discomfort.

Review of local safety assessments of the nasal cavity and olfactory nerve function did not raise any safety concerns.

Dr. Khachikyan concluded that the nasal irritation assessment tool and monitoring are adequate to evaluate the potential for local toxicity. Most subjects had no nasal irritation. Erosions were not observed in any subjects. One subject had minor bleeding that resolved within a minute with no intervention. Seven subjects reported nasal irritation after 8 mg nasal naloxone with 20% of alcohol. The risk is acceptable given the potentially life-saving benefits of this medication. The Applicant will be advised to add a description of the nasal irritation observed in the studies in the product label.

One subject had a treatment-emergent abnormal olfactory test result after the introduction of the study drug. The abnormal result was after receiving the (b)(4)% alcohol formulation and not the 20% alcohol formulation that is proposed for marketing. Olfactory test results do not raise any significant safety concerns.

The Applicant submitted a literature review to support the safety of the systemic exposures observed with 8 mg naloxone. The previous finding of safety for Narcan in adults covers the

Cmax observed in the pharmacokinetic studies. However, the AUC observed exceeded that of the reference product and thus the pharmacokinetic study data do not provide a scientific bridge to the previous Agency finding of safety for Narcan. The literature, as summarized in the Applicant's Summary of Clinical Safety section 5.10, support the safety of naloxone at doses that would be expected to result in exposures far exceeding those observed for naloxone nasal spray. Severe opioid withdrawal in the setting of reversing opioid overdose is a known risk for patients physically dependent on opioids. The severity of the withdrawal may be associated with dose. Also, a 2020 publication in Annals of Emergency Medicine[1] has reported an association of higher out-of-hospital naloxone doses with higher incidence of pulmonary complications after overdose. However, these potential safety concerns are still outweighed by the benefit of reversing a life-threatening overdose. 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 nasal spray 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 by the intravenous route.

11. Advisory Committee Meeting

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

12. Pediatrics

The final Division of Pediatric and Maternal Health pediatric consult review is pending. Narcan is approved for use in the entire pediatric age range. Because naloxone nasal spray represents a change in the dosing regimen from weight-based in the reference Narcan label to an 8 mg fixed dose, the Applicant is required to conduct a pediatric assessment under the Pediatric Research Equity Act (PREA). The preliminary conclusion of the pediatric review team is that given the one-time use in an emergency setting with negative findings on the juvenile animal studies and acceptable safety profile, the risk benefit of this product for pediatric patients down to birth is favorable. The application was discussed at the January 28, 2020 Pediatric Review Committee Meeting and the Committee agreed with the review team that the pediatric assessment was adequate to support approval of this product for pediatric patients down to birth.

13. Other Relevant Regulatory Issues

- Not applicable

[1] Ann Emerg Med. 2020 Jan;75(1):39-48. doi: 10.1016/j.annemergmed.2019.04.006. Epub 2019 Jun 8. Pulmonary Complications of Opioid Overdose Treated With Naloxone

14. Labeling

The DMEPA review of the container label, carton labeling, and Instructions for Use have been deferred pending submission of the results of the Human Factors validation study. Dr. Cameron Johnson and Dr. Otto Townsend of DMEPA provided recommendations on the proposed proprietary name and prescribing information. The proposed proprietary name was found not to be acceptable because it is vulnerable to name confusion.

Additionally, the Division of Pediatric and Maternal Health (DPMH) was consulted regarding the proposed pregnancy, lactation, and pediatric sections of labeling. DPMH provided recommendations for the proposed labeling.

Labeling is ongoing at the time of this writing, and specific recommendations have been made in the relevant sections of this review.

15. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A REMS is not recommended at this time.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No PMRs or PMCs are recommended at this time.

16. Recommended Comments to the Applicant

Refer to the Integrated Quality Assessment for a list of Product Quality deficiencies to be included in the Complete Response Letter.

1. Results of a human factors validation study are required to inform the safe use and labeling of the product. The human factors validation study must demonstrate that the final finished combination product user interface will maximize the likelihood that the product will be safely and effectively used by intended users.
   Provide the results of the human factors validation study and updated labeling.

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/s/

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