

FDA Briefing Document

**Joint Meeting of Anesthetic and Analgesic Drug Products Advisory
Committee and Drug Safety and Risk Management Advisory Committee**

October 5, 2016

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought information and data regarding naloxone to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee

October 5, 2016

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DIVISION DIRECTOR MEMO

FDA CENTER FOR DRUG EVALUATION AND RESEARCH DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

MEMORANDUM

DATE: September 9, 2016

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Overview of the October 5, 2016 AADPAC/DSaRM Meeting to Discuss
Naloxone Products Intended for Use in the Community.

The increasing incidence of misuse and abuse of illicit and prescription opioids and the associated risks of addiction, overdose, and death is a public health crisis in the United States. Opioid overdose is characterized by life threatening respiratory and central nervous system depression that, if not immediately treated, may lead to significant morbidity and mortality. Drug overdose is currently the leading cause of accidental death in the US and opioids, primarily prescription pain relievers and heroin, are the main drugs associated with overdose deaths accounting for 61% of all drug overdose deaths in 2014.^{1,2} When administered quickly after an opioid overdose, naloxone, an opioid antagonist, can save lives. Many organizations and local municipalities across the US have developed programs for making naloxone available in the community.³ These programs have traditionally relied on the off-label use of commercially available naloxone solution in pre-packaged kits using a commercially available nasal atomizer device and syringe for administration by the intranasal route, and less frequently, using a needle and syringe for administration by the intramuscular route. Also, there is generally training provided on how and when to use these kits. While there is anecdotal evidence of efficacy for

¹ CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2015. Available at <http://wonder.cdc.gov>.

² Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014. MMWR 64(50); 1378-82, January 1, 2016

³ Wheeler E, Jones TS, Gilbert MK, Davidson, PJ. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons – United States, 2014. MMWR 64(23); 631-635, June 19, 2015

these kits in reversing opioid overdoses, there are little data about the pharmacokinetic profile of naloxone when administered intranasally by these kits or the frequency of failure to reverse opioid overdose.

Expanded access to naloxone in the community is one component of the Commissioner's Opioid Action Plan which outlines FDA's addressing the epidemic of opioid abuse, addiction, and overdose.⁴ FDA has developed an approach to development of naloxone products for use in the community relying on the Agency's prior findings of safety and efficacy for Narcan (naloxone hydrochloride; NDA 16636) and by a demonstration of bioequivalence with no less than the minimum dose of Narcan, 0.4 mg by intravenous, intramuscular, or subcutaneous route.⁵ This reflects the ethical challenges associated with conducting clinical studies in patients with actual or induced opioid overdose when known effective doses of naloxone are available. In addition, Sponsors are asked to provide studies demonstrating that laypersons can understand how to administer the product correctly using the supplied instructions for use. There have been two public meetings to discuss the development of naloxone for use in the community, one in 2012 and one in 2015. In addition, FDA has utilized various expedited programs for serious conditions to facilitate the development, review, and approval of naloxone products intended for use in the community.

As a result of these efforts, two naloxone products intended for use in the community have been approved for use in adult and pediatric patients. 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 (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. Both products are packaged with two devices in a carton, in the event repeat administration is required.

In patients managed with opioid analgesics, an opioid overdose leading to death can occur in a variety of settings. Patients may inadvertently take too much opioid analgesic trying to better manage pain, or through mistakes in dose or frequency. Initiating a new concomitant medication that inhibits the metabolic pathway of an opioid or discontinuation of a concomitant medication that induces the metabolic pathway can result in overdose in a patient who has used their opioid analgesic according to instructions. Addition of a new medication that is a central nervous system depressant, or an error in judgment surrounding the use of alcohol, can result in serious respiratory depression in a patient previously stable on an opioid. Overdose can occur in the household of a patient prescribed opioids by accidental exposure by a child or through intentional misuse or abuse by family members or friends. Individuals abusing prescription opioid analgesics or illicit opioids can also inadvertently overdose due to unfamiliarity with the drugs or errors in judging how much can be tolerated. Depending on the situation, death from overdose can occur with the first attempt at abuse of an opioid.

⁴ <http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm>

⁵ Narcan (naloxone hydrochloride) injection prescribing information accessed at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/016636s052s054lbl.pdf

With these scenarios in mind, the indication for the naloxone products intended for use in the community^{6,7} was developed not just with the basic indication statement, “for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression”, but also with the following statement, “Intended for immediate administration as emergency therapy in settings where opioids may be present.” The indication intentionally does not specify the source of the opioid, i.e. prescription or illicitly obtained, or the dose, recognizing that opioid overdoses occur in many situations involving patients with prescribed opioids and non-patients, and that many factors influence whether any particular dose can result in an overdose, e.g. age, size, prior opioid use. The last statement in the indication, “Not a substitute for emergency medical care” is to emphasize the importance of pursuing medical treatment use of naloxone so that the individual can be assessed for risk of recurrent respiratory depression if the effect of the opioid is expected to outlast the effect of naloxone and for any other evidence of harm associated with the overdose.

During this meeting, you will hear presentations from Agency staff about the work that has been done to develop naloxone products for use in the community including what is known about the safety of using naloxone and the risk of precipitating an acute opioid withdrawal syndrome, the concerns specific to dosing in pediatric patients, the clinical pharmacology of naloxone and information about the use of naloxone.

We will ask for your advice on whether the current minimum standard for approval is adequate, and if higher doses are recommended, how to weigh the need for efficacy against the risk of precipitating an acute withdrawal syndrome. We will also ask you for advice about the naloxone dosing for pediatric patients and how to integrate that into these programs. Also, as more products are under development and seek marketing approval, we will ask your advice on whether there is benefit in having different doses for the same or different products and how a clinician can determine which product to prescribe. Additionally, we will seek your advice about the utility of products that require assembly or more than basic instructions for use.

For your reference, we have included the following materials in this background package:

- Approved labeling for Evzio and Narcan Nasal Spray
- Approved labeling for Narcan (original product for injection)
- FDA reviews for Evzio (Summary and Cross-Discipline Team Leader) and Narcan Nasal Spray (Summary and Cross-Discipline Team Leader)
- Summary report for 2012 and 2015 naloxone public meetings

⁶ Evzio (naloxone hydrochloride) injection prescribing information, accessed at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205787Orig1s000lbl.pdf

⁷ Narcan (naloxone hydrochloride) nasal spray prescribing information accessed at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208411lbl.pdf

DRAFT POINTS FOR DISCUSSION

1. The current pharmacokinetic standard for the approval of naloxone products for use in the community requires demonstration of comparable or greater naloxone levels compared to a minimum dose of 0.4 mg of approved naloxone injection administered by one of the labeled routes of administration.
 - a. If you support a different pharmacokinetic standard, describe the rationale for this approach.
 - b. Discuss whether this minimum standard for approval is sufficient to address the management of the variety of opioid overdose situations arising in the community or if there is a role for more than one standard for different anticipated situations, e.g., for patients prescribed opioids vs. illicit use of opioids, for overdoses expected to involve partial agonists vs. full agonists, for situations with possible exposure to higher potency opioids (carfentanil-laced heroin). Include a discussion of how such an approach could be implemented.
2. Different sponsors have proposed different strength doses for their naloxone products intended for use in the community (that meet or exceed the minimum pharmacokinetic standard), and some have proposed marketing more than one dose strength. Discuss whether there are factors that support different dosing strengths, and how that can be reflected in labeling to assist clinicians in product selection.
3. Both children and adults may be at risk for opioid overdose in the home. The current approach has been to require that naloxone products for community use are appropriate for both adult and pediatric use to minimize the risk of product confusion when treating an overdose in the home. Strictly following the pediatric dosing recommendations from the American Academy of Pediatrics (AAP) would require a minimum dose of 2 mg, higher than the current standard for adult products.
 - a. Discuss whether there should be products specifically targeting naloxone dosing for children based on the AAP recommendations.
 - b. Discuss whether the standard for approval of naloxone products for use in the community should reflect pediatric dose requirements, and comment on the implications for use of these products in adults.
 - c. Discuss whether it is acceptable to have different adult and pediatric products available in the home, and how to weigh the risk for product confusion.

4. There is a tension in balancing the need for rapid reversal of an opioid overdose to avoid permanent hypoxic injury to the brain and for avoiding complications from precipitated opioid withdrawal in opioid-tolerant patients. In controlled settings with adequate ventilatory support, naloxone can be titrated to effect. In the community, there is a five to 10 minute window before hypoxic injury is irreversible and adequate ventilatory support is often not available.
 - a. Discuss whether the Division should consider concerns of opioid withdrawal with naloxone use in the community to treat opioid overdose.
5. Is the pharmacokinetic standard based on 0.4 mg of naloxone given intramuscularly appropriate for approval of naloxone products for use in the community or are higher doses and/or exposures required?
6. As part of the standard for approval, the approved naloxone products for use in the community have Instructions for Use (IFU) suitable for use by laypersons as supported by human factors studies. The naloxone kits assembled with naloxone solution for injection and various syringe/nasal atomizer devices may have written instructions and are generally accompanied by hands on training. Discuss whether it is acceptable to approve new products intended for use in the community that require training beyond the IFU.



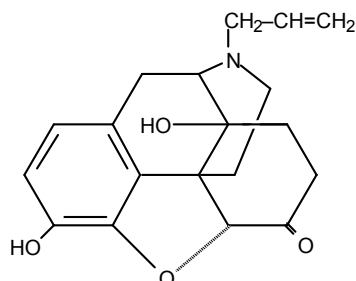
NARCAN[®]
(Naloxone Hydrochloride Injection, USP)

Opioid Antagonist


R_x only

DESCRIPTION

NARCAN (naloxone hydrochloride injection, USP), an opioid antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



•HCl

NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5 α -epoxy-3, 14 - dihydroxy 
morphinan-6-one hydrochloride

Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

NARCAN injection is available as a sterile solution for intravenous, intramuscular and subcutaneous administration in three concentrations: 0.02 mg, 0.4 mg and 1 mg of naloxone hydrochloride per mL.

pH is adjusted to 3.5 ± 0.5 with hydrochloric acid.

The 0.02 mg/mL strength is an unpreserved, paraben-free formulation containing 9 mg/mL sodium chloride.

The 0.4 mg/mL vial contains 8.6 mg/mL of sodium chloride and 2 mg/mL of methylparaben and propylparaben as preservatives in a ratio of 9:1. The 0.4 mg/mL ampul is also available in an unpreserved, paraben-free formulation containing 9 mg/mL of sodium chloride.

The 1 mg/mL vial contains 8.35 mg/mL of sodium chloride and 2 mg/mL of methylparaben and propylparaben as preservatives in a ratio of 9:1. The 1 mg/mL ampul is also available in an unpreserved, paraben-free formulation containing 9 mg/mL of sodium chloride.

CLINICAL PHARMACOLOGY

Complete or Partial Reversal of Opioid Depression

NARCAN prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension. Also, NARCAN can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

NARCAN is an essentially pure opioid antagonist, i.e., it does not possess the “agonistic” or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.

NARCAN has not been shown to produce tolerance or cause physical or psychological dependence. In the presence of physical dependence on opioids, NARCAN will produce withdrawal symptoms. However, in the presence of opioid dependence, opiate withdrawal symptoms may appear within minutes of NARCAN administration and subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of NARCAN and to the degree and type of opioid dependence. While the mechanism of action of NARCAN is not fully understood, *in vitro* evidence suggests that NARCAN antagonizes opioid effects by competing for the μ , κ and σ opiate receptor sites in the CNS, with the greatest affinity for the μ receptor.

When NARCAN is administered intravenously (I.V.), the onset of action is generally apparent within two minutes. The onset of action is slightly less rapid when it is administered subcutaneously (S.C.) or intramuscularly (I.M.). The duration of action is dependent upon the dose and route of administration of NARCAN. Intramuscular administration produces a more prolonged effect than intravenous administration. Since the duration of action of NARCAN may be shorter than that of some opiates, the effects of the opiate may return as the effects of NARCAN dissipates. The requirement for repeat doses of NARCAN will also be dependent upon the amount, type and route of administration of the opioid being antagonized.

Adjunctive Use in Septic Shock

NARCAN has been shown in some cases of septic shock to produce a rise in blood pressure that may last up to several hours; however, this pressor response has not been demonstrated to improve patient survival. In some studies, treatment with NARCAN in the setting of septic shock has been associated with adverse effects, including agitation, nausea and vomiting, pulmonary edema, hypotension, cardiac arrhythmias, and seizures. The decision to use NARCAN in septic shock should be exercised with caution, particularly in patients who may have underlying pain or have previously received opioid therapy and may have developed opioid tolerance.

Because of the limited number of patients who have been treated, optimal dosage and treatment regimens have not been established.

PHARMACOKINETICS

Distribution

Following parenteral administration, NARCAN is rapidly distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

Metabolism and Elimination

NARCAN is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucuronide as the major metabolite. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours. After an oral or intravenous dose, about 25-40% of the drug is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

INDICATIONS AND USAGE

NARCAN is indicated 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 is also indicated for diagnosis of suspected or known acute opioid overdose.

NARCAN may be useful as an adjunctive agent to increase blood pressure in the management of septic shock (see **CLINICAL PHARMACOLOGY; Adjunctive Use in Septic Shock**).

CONTRAINDICATIONS

NARCAN is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients in NARCAN.

WARNINGS

Drug Dependence

NARCAN should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include, but are not limited to, the following: 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. In the neonate, opioid withdrawal may also include: convulsions, excessive crying, and hyperactive reflexes.

Repeat Administration

The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some opioids may exceed that of NARCAN.

Respiratory Depression due to Other Drugs

NARCAN is not effective against respiratory depression due to non-opioid drugs and in the management of acute toxicity caused by levopropoxyphene. Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete or require higher doses of naloxone. If an incomplete response occurs, respirations should be mechanically assisted as clinically indicated.

PRECAUTIONS

General

In addition to NARCAN, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute opioid poisoning.

Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death. Excessive doses of NARCAN in postoperative patients may result in significant reversal of analgesia and may cause agitation (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION; Usage in Adults-Postoperative Opioid Depression**). Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation, and pulmonary edema. It has been suggested that the pathogenesis of pulmonary edema associated with the use of NARCAN is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

Drug Interactions

Large doses of naloxone are required to antagonize buprenorphine since the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression. The barbiturate methohexital appears to block the acute onset of withdrawal symptoms induced by naloxone in opiate addicts.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals to assess the carcinogenic potential of NARCAN have not been conducted. NARCAN was weakly positive in the Ames mutagenicity and in the *in vitro* human lymphocyte chromosome aberration test but was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in the *in vivo* rat bone marrow chromosome aberration study. Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to NARCAN.

Use in Pregnancy

Teratogenic Effects: Pregnancy Category C:

Teratology studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to NARCAN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NARCAN should be used during pregnancy only if clearly needed.

Non-teratogenic Effects:

Risk-benefit must be considered before NARCAN is administered to a pregnant woman who is known or suspected to be opioid-dependent since maternal dependence may often be accompanied by fetal dependence. Naloxone crosses the placenta, and may precipitate withdrawal in the fetus as well as in the mother. Patients with mild to moderate hypertension who receive naloxone during labor should be carefully monitored as severe hypertension may occur.

Use in Labor and Delivery

It is not known if NARCAN (naloxone hydrochloride injection, USP) affects the duration of labor and/or delivery. However, published reports indicated that administration of naloxone during labor did not adversely affect maternal or neonatal status.

Nursing Mothers

It is not known whether NARCAN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NARCAN is administered to a nursing woman.

Pediatric Use

NARCAN (naloxone hydrochloride injection, USP) may be administered intravenously, intramuscularly or subcutaneously in children and neonates to reverse the effects of opiates. The American Academy of Pediatrics, however, does not endorse subcutaneous or intramuscular administration in opiate intoxication since absorption may be erratic or delayed. Although the opiate-intoxicated child responds dramatically to NARCAN, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.

When NARCAN is given to the mother shortly before delivery, the duration of its effect lasts only for the first two hours of neonatal life. It is preferable to administer NARCAN

directly to the neonate if needed after delivery. NARCAN has no apparent benefit as an additional method of resuscitation in the newly born infant with intrauterine asphyxia which is not related to opioid use.

Usage in Pediatric Patients and Neonates for Septic Shock:

The safety and effectiveness of NARCAN in the treatment of hypotension in pediatric patients and neonates with septic shock have not been established. One study of two neonates in septic shock reported a positive pressor response; however, one patient subsequently died after intractable seizures.

Geriatric Use

Clinical studies of NARCAN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Insufficiency/Failure

The safety and effectiveness of NARCAN in patients with renal insufficiency/failure have not been established in well-controlled clinical trials. Caution should be exercised when NARCAN is administered to this patient population.

Liver Disease

The safety and effectiveness of NARCAN in patients with liver disease have not been established in well-controlled clinical trials. Caution should be exercised when NARCAN is administered to patients with liver disease.

ADVERSE REACTIONS

Postoperative

The following adverse events have been associated with the use of NARCAN in postoperative patients: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of NARCAN in postoperative patients may result in significant reversal of analgesia and may cause agitation (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION; Usage in Adults-Postoperative Opioid Depression**).

Opioid Depression

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death (see **PRECAUTIONS**).

Opioid Dependence

Abrupt reversal of opioid effects in persons who are physically dependent on opioids may precipitate an acute withdrawal syndrome which may include, but is not limited to, the

following signs and symptoms: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal may also include: convulsions; excessive crying; hyperactive reflexes (see **WARNINGS**).

Adverse events associated with the postoperative use of NARCAN are listed by organ system and in decreasing order of frequency as follows:

Cardiac Disorders: pulmonary edema, cardiac arrest or failure, tachycardia, ventricular fibrillation, and ventricular tachycardia. Death, coma, and encephalopathy have been reported as sequelae of these events.

Gastrointestinal Disorders: vomiting, nausea

Nervous System Disorders: convulsions, paraesthesia, grand mal convulsion

Psychiatric Disorders: agitation, hallucination, tremulousness

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, respiratory depression, hypoxia

Skin and Subcutaneous Tissue Disorders: nonspecific injection site reactions, sweating

Vascular Disorders: hypertension, hypotension, hot flushes or flushing.

See also **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**; **Usage in Adults**; **Postoperative Opioid Depression**.

DRUG ABUSE AND DEPENDENCE

NARCAN is an opioid antagonist. Physical dependence associated with the use of NARCAN has not been reported. Tolerance to the opioid antagonist effect of NARCAN is not known to occur.

OVERDOSAGE

There is limited clinical experience with NARCAN overdosage in humans.

Adult Patients

In one small study, volunteers who received 24 mg/70 kg did not demonstrate toxicity. In another study, 36 patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m²/min) of NARCAN followed immediately by 2 mg/kg/hr for 24 hours. Twenty-three patients experienced adverse events associated with naloxone use, and naloxone was discontinued in seven patients because of adverse effects. The most serious adverse events were: seizures (2 patients), severe hypertension (1), and hypotension and/or bradycardia (3).

At doses of 2 mg/kg in normal subjects, cognitive impairment and behavioral symptoms, including irritability, anxiety, tension, suspiciousness, sadness, difficulty concentrating, and lack of appetite have been reported. In addition, somatic symptoms, including dizziness, heaviness, sweating, nausea, and stomachaches were also reported. Although complete information is not available, behavioral symptoms were reported to often persist for 2-3 days.

Pediatric Patients

Up to 11 doses of 0.2 mg of naloxone (2.2 mg) have been administered to children following overdose of diphenoxylate hydrochloride with atropine sulfate. Pediatric reports include a 2-1/2 year-old child who inadvertently received a dose of 20 mg of naloxone for treatment of respiratory depression following overdose with diphenoxylate hydrochloride with atropine sulfate. The child responded well and recovered without adverse sequelae. There is also a report of a 4-1/2 year-old child who received 11 doses during a 12-hour period, with no adverse sequelae.

Patient Management

Patients who experience a NARCAN overdose should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control center for the most up-to-date patient management information.

DOSAGE AND ADMINISTRATION

NARCAN may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration, which is recommended in emergency situations.

Since the duration of action of some opioids may exceed that of NARCAN, the patient should be kept under continued surveillance. Repeated doses of NARCAN should be administered, as necessary.

Intravenous Infusion

NARCAN may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2 mg of NARCAN in 500 mL of either solution provides a concentration of 0.004 mg/mL. Mixtures should be used within 24 hours. After 24 hours, the remaining unused mixture must be discarded. The rate of administration should be titrated in accordance with the patient's response.

NARCAN should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to NARCAN unless its effect on the chemical and physical stability of the solution has first been established.

General

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Usage in Adults

Opioid Overdose—Known or Suspected:

An initial dose of 0.4 mg to 2 mg of NARCAN may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions are not obtained, it may be repeated at two- to three-minute intervals. If no response is observed after 10 mg of NARCAN have been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Opioid Depression:

For the partial reversal of opioid depression following the use of opioids during surgery, smaller doses of NARCAN are usually sufficient. The dose of NARCAN should be titrated according to the patient's response. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.1 to 0.2 mg intravenously at two- to three-minute intervals to the desired degree of reversal, i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of NARCAN may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of NARCAN may be required within one- to two-hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of an opioid. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

Septic Shock:

The optimal dosage of NARCAN or duration of therapy for the treatment of hypotension in septic shock patients has not been established (see **CLINICAL PHARMACOLOGY**).

Usage in Children

Opioid Overdose—Known or Suspected:

The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, NARCAN may be administered I.M. or S.C. in divided doses. If necessary, NARCAN can be diluted with sterile water for injection.

Postoperative Opioid Depression:

Follow the recommendations and cautions under **Adult Postoperative Depression**. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.005 mg to 0.01 mg intravenously at two- to three-minute intervals to the desired degree of reversal.

Usage in Neonates

Opioid-induced Depression:

The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines for postoperative opioid depression.

HOW SUPPLIED

NARCAN (naloxone hydrochloride injection, USP) for intravenous, intramuscular, and subcutaneous administration is available as:

Multiple Dose Vials

0.4 mg/mL	10 mL multiple dose vial-box of 1, NDC 63481-365-05
1 mg/mL	10 mL multiple dose vial-box of 1, NDC 63481-368-05

Preservative-Free Ampules

0.02 mg/mL	2 mL unit dose ampule-box of 10, NDC 63481-359-10
0.4 mg/mL	1 mL unit dose ampule-box of 10, NDC 63481-358-10
1 mg/mL	2 mL unit dose ampule-box of 10, NDC 63481-377-10

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]. Protect from light.

Store in carton until contents have been used.

Manufactured for:

Endo Pharmaceuticals Inc.

Chadds Ford, Pennsylvania 19317



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Printed in U.S.A.

51-022523-00/July, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205787Orig1s000

SUMMARY REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

Summary Review for Regulatory Action

Date	April 3, 2014
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	205787
Applicant Name	Kaleo, Inc.
Date of Submission	December 20, 2013
PDUFA Goal Date	June 20, 2014
Proprietary Name / Established (USAN) Name	Evzio Naloxone HCl injection
Dosage Forms / Strength	0.4 mg/0.4 mL
Proposed Indication	<ul style="list-style-type: none">• Evzio is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.• Evzio is intended for immediate administration as emergency therapy in settings where opioids may be present.• Evzio is not a substitute for emergency medical care.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL	Sharon Hertz, MD
Medical Officer Review	Steven Galati, MD, Josh Lloyd, MD
Pharmacology Toxicology Review	Carlic Huynh, PhD, R. Daniel Mellon, PhD
CMC Review/OBP Review	Ying Wang, PhD, Julia Pinto, PhD, Prasa Peri, PhD
ONDQA Microbiology Review	Jessica Cole, PhD, Bryan Riley, PhD
Clinical Pharmacology Review	Wei Qiu, PhD, Yun Xu, PhD
CDRH REGODB/DMQ/OC GHDB/ DAGID/ODE ODE/DAGRID	M. Isabel Tejero del Rio, MD, PhD; Carl Fischer, PhD Lana Shiu, M.D., Keith Marin, QuynhNhu Nguyen, Ron Kaye
OSI DBGC	Chase Bourke, PhD, Charles Bonapace, PharmD, William Taylor, PhD
OC/OMPQ	Juandria Williams
OSE/DMEPA	Vicky Borders-Hemphill, PharmD, Morgan Walker, PharmD, Kellie Taylor, PharmD, MPH. Irene Chan, PharmD, BCPS
OND/SEALD	Abimbola Adebawale, Eric Brodsky, MD
OPDP/DCDP	L. Sheneé Toombs, Olga Salis, Michale Wade
OMP/DMPP	Karen Dowdy, RN, BSN, Sharon Mills, BSN, RN, CCRP, L. Sheneé' Toombs, PharmD, Barbara Fuller, RN, MSN, CWOCN, LaShawn Griffiths, MSHS-PH, BSN, RN
Pediatric and Maternal Health Staff Review	Erica Wynn, MD, MPH, Hari Sachs, MD, Lynne Yao, MD.

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Errors Prevention
 OPDP=Office of Prescription Drug Promotion
 DCDP=Division of Consumer Drug Promotion
 OMP=Office of Medical Policy Initiatives
 DMPP=Division of Medical Policy Programs
 OSI=Office of Scientific Investigations
 CDTL=Cross Discipline Team Leader
 ONDQA=Office of New Drug Quality Assessment
 OC=Office of Compliance
 OMPQ=Office of Manufacturing and Product Quality

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 Evzio
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1. Introduction

The Applicant has submitted this NDA in support of marketing approval for Evzio, their naloxone autoinjector designed for use in nonmedical settings to reverse opioid overdose due to either accidental or intentional overdose. Evzio is a single-injection, fixed-dose, (b) (4) autoinjector that is designed to deliver 0.4 mg of naloxone HCl intramuscularly or subcutaneously. The unit incorporates both audio and visual instructions and cues to guide the person administering the drug during a medical emergency and is appropriate for administration by non-medically trained individuals. This application was submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and references NDA 016636 for the approved product Narcan.

2. Background

Naloxone was first approved in 1971 to reverse opioid intoxication or overdose. It is widely used both by hospital and first responder personnel. With the increasing medical use of opioid analgesics, and the increasing misuse and abuse of these drugs, there has been a marked increase in opioid overdose in both the pain patient and addiction patient populations. As it is frequently successful in reversing even severe opioid overdoses, naloxone has been increasingly used by non-health care professionals, including family, friends and other caregivers. A number of jurisdictions across the US have begun providing naloxone to patients, and providing instruction for its use to the patients' family, friends and/or caregivers. However, as the products are only available in glass vials and ampules, they are distributed with syringes and needles for manual injection, or with syringes and atomizers for nasal administration. Nasal administration is an unapproved route which could require higher doses than the approved routes if the bioavailability is different. These "kits" can be lifesaving, but they are more difficult to use than an autoinjector for most lay people. The addition of this easy to use product, with little to no associated risk, would be of potentially great public health importance.

Given the fact that it would be infeasible to perform a clinical efficacy study, and given the vast clinical experience with naloxone, the Division of Anesthesia, Analgesia, and Addiction Products agreed that the evidentiary basis for efficacy and safety could be the submission of a single, pivotal bioequivalence study that demonstrated comparable pharmacokinetics between the novel formulation and a generic naloxone product, (as the NDA product is no longer marketed), delivered by an approved route of administration. The Applicant has submitted such a study, and the review team has determined that it does, indeed, demonstrate bioequivalence between the products. In addition, the Agency required the evaluation of the safety and efficacy of the device, and a human factors validation

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study, both of which were completed by the Applicant and submitted with the NDA. The results of those studies are discussed below.

3. CMC

The following has been reproduced from pages 4 through 10 of Dr. Hertz's review:

Dr. Ying Wang performed the review of the drug substance and drug product. The information for the drug substance is referenced in DMF (b) (4) for which (b) (4) is the holder. According to Dr. Wang, the drug substance specifications mostly follow the USP and EP monographs and additional specifications for related substance meet the criteria in the ICH Q3A guideline. The drug product constituent component, 0.4 mg naloxone hydrochloride in an (b) (4) filled into a Type I (b) (4) glass cartridge (i.e., primary container closure), has the same formulation as a listed drug product (International Medicinal Systems, Naloxone HCl Injection, USP [1 mg/mL]. The only excipients are sodium hydrochloride, hydrochloric acid, and water. The drug product batches for the clinical study and registration stability lots meet the specifications.

The container closure system include the glass cartridge, a Type I (b) (4) gray (b) (4) rubber plunger which has contact with the drug solution, and an aluminum-crimping cap which does not have contact with the drug solution. The materials in contact with the drug solution comply with the USP and European Pharmacopoeia and are suitable for the storage of sterile drug product solution. An extractables study was completed with the rubber plungers and seals using a placebo of the drug product solution placebo (NaCl, pH 3.4) and isopropanol, as a control solvent. No significant peaks from the plunger or seals were observed.

The drug product was stable during stability testing with relatively low impurity levels. The Applicant submitted 12 months of stability data under term storage conditions (25°C/60% RH), 6 months under intermediate storage conditions (30°C/65% RH), and 6 month accelerated storage condition (40°C/75% RH) are provided in the submission. The stability data support the proposed expiry of the earlier of either 27 months from the manufacturing date for the drug constituent component of EVZIO or 24 months from the date of final assembly, packaging, and labeling of EVZIO.

The drug constituent component manufacturing sites were all found to be acceptable by the CDER Office of Compliance.

The Applicant was granted a categorical exclusion for the environmental assessment based on the rationale that there would be a very low estimated concentration of drug substance at point of entry into the aquatic environment.

Dr. Jessica Cole conducted the product quality microbiology review. The drug is (b) (4) and filled into a glass cartridge. The filled glass cartridge is assembled with the needle and protective sheath. This cartridge assembly is (b) (4). Dr. Cole found the response to requested information adequate and the Applicant agreed to a request amendment to the specification for endotoxin to (b) (4) EU/mg naloxone to prevent potential pyrogenic reactions in infants.

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The CDRH engineering review was conducted by Lana Shiu, MD. The device is a user-operated, (b) (4), needle-based system with audible and visual cues to guide the user through administration once the device is removed from its outer case. The Drug Cartridge container closure system for the naloxone drug product consists of a Type 1 (b) (4) glass Cartridge with an (b) (4) Plunger and an aluminum Crimp Cap lined with an (b) (4). When activated, the device injects a single dose of 0.4 mL (0.4 mg of naloxone HCl).



The total needle length is 5/8 of an inch and 1/4 of an inch extends outside the device upon actuation. The needle is fully retracted into the device housing after use. (b) (4). (b) (4) make contact with the drug product or injection site at any time.

(b) (4)

(b) (4)

As noted by Dr. Shiu (p. 4):

Under dosing is prevented (b) (4)

The Volume Dispensed is defined as a release specification to ensure dosing accuracy.

In addition, (b) (4). The activation, needle penetration, drug injection and retraction of the needle occur in less than five seconds, and of that time, the actual needle penetration and drug injection time is (b) (4). A red safety guard prevents accidental activation of the injection.

Also noted by Dr. Shiu (p.6):

(b) (4)

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Intelliject (device developer for both NAI and EAI) relied on the prior validation study of EAI to support NAI development plan. CDRH provided the engineering device consult on the autoinjector and its software during the review of EAI (epiCard) during the IND 76367 as well as during the NDA 201739.

Device design, materials of construction, biocompatibility, sterilization, and shelf-life expectancy are consistent with that of IND 76367/NDA201739.

Per FDA's 2005 Guidance: *Medical Devices with Sharps Injury Prevention Features*, 500 NAI devices were tested *in-vitro* to confirm needle retraction. All 500 devices passed needle retraction testing, further verifying the NAI retractable needle feature as described in report IJ-731R-03O.

Dr. Shiu concluded that safety and efficacy have been demonstrated in this device.

The CDRH Human Factors and Device Use review was conducted by Ms. Quynh Nhu Nguyen. Preliminary and formative studies were conducted to optimize labeling, instructions for use and device design user interface. A human factors validation study was conducted with 40 participants, consisting of 19 juveniles and 21 adults, asked to deliver a simulated injection without training. Ms. Nguyen noted the following (p. 4):

The following sections provide a discussion on the observed use errors and difficulties which included the four issues identified above:

- Five juvenile participants used the trainer instead of study device but post-test user interview showed that these participants confirmed that they knew which device was which, and stated that they used the trainer intentionally because the simulation as a test or pretend situation.
- Four juvenile participants experienced difficulty with pulling off red safety guard. Intelliject confirmed that all adult participants could remove the red safety guard, and four juvenile participants experienced some difficulty initially but were able to pull it off.
- Four adult participants and two juvenile participants did not inject into the outer thigh but instead, they injected into the front or back of the thigh, inner thigh, etc. Intelliject confirmed that NAI is indicated for subcutaneous or intramuscular administration. While Intelliject has determined that the outer thigh is the ideal injection site location, if NAI were to be administered into the thigh, legs or upper arms/shoulder, they stated that the patient would still receive a SC or IM injection.
- Two participants (one adult and one juvenile) did not press device firmly against the skin for device activation. Based on post-test interview responses, Intelliject considered changes to the voice script to emphasize the need to push harder, and to wait until a click is heard. However, Intelliject believes that if a user commits a critical use error, the residual risk is that the

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patient would be receiving the current standard of care from paramedic and EMT personnel.

- Two juvenile participants did not hold the device in place for at least 1 second. Intelliject confirmed that the injection time of the needle and dispensing time of the drug is less than (b) (4). In addition, the voice prompt provides a device count down “five, four, three, two, one” after the injection is initiated.

Ms. Nguyen concluded that the results of the human factors study were acceptable, and no further optimization on the design and/or labeling was necessary.

The CDRH Office of Compliance review was conducted by Dr. Isabel Tejero del Rio. A number of deficiencies were identified and submitted to the Applicant following her initial review dated January 21, 2014. In a memo dated February 18, 2014, Dr. Tejero noted that the Applicant’s response to the deficiency letter dated January 22, 2014, was adequate with no residual deficiencies. Two facilities were identified as being subject to applicable Medical Device Regulations under 21 CFR Part 820. One site, Kaléo Inc., had an inspection on June 27, 2011, that was classified no action indicated (NAI). The second site, (b) (4)

Therefore, although an inspection under the Medical Device regulation on (b) (4), was classified NAI, a recommendation was made for a pre-approval inspection for compliance with 21 CFR Part 820. Dr. Tejero did note the following (p. 4):

However, CDRH/OC would consider acceptable a post-market inspection of the (b) (4) facility due to the public health benefit of the rapid approval of Evzio naloxone autoinjector, and based on the adequate desk review and previous NAI inspections of two (b) (4)

A form FDA-483 was issued for the (b) (4) site with three observations. The first observation was that the firm was (b) (4)

The Applicant responded that they were awaiting the final labeling from FDA prior to completing (b) (4). The required documentation to complete a desk review of the (b) (4) assembly line and investigators were able to observe the line in action and found no deficiencies.

The next two observations were:

OBSERVATION 2: Process control procedures that describe any process controls necessary to ensure conformance to specifications have not been adequately established. Specifically:

- A. The firm is not currently (b) (4) in that they have not completed the performance qualification for (b) (4)

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(b) (4)

Qualification of the controlled environment areas is required before the firm may proceed with the commercial scale process performance qualification (PPQ) batches.

B. The equipment qualification protocol, (b) (4)

Evaluation: The investigator stated during the March 21st call that the firm (b) (4)

The investigator indicated that she did not have any major concerns respect to the qualification process. Furthermore, the investigator believed that (b) (4) could be completed within a week, as indicated by the firm.

OBSERVATION 3: Procedures for corrective and preventive action have not been adequately established. Specifically,

(b) (4)

Evaluation: the investigator stated during the phone call of March 21st that this observation had been corrected before they closed the inspection. Thus, CDRH/OC has no additional concerns regarding the issue.

Dr. Tejero concluded that, based on the nature of the observations cited in form FDA-483, in conjunction with discussions with the investigators, district office, the CDER Office of Compliance and the CDRH Office of Compliance, the inspection was classified Voluntary Action Indicated and that in conjunction with a satisfactory desk review of the NDA, adequate inspectional history of (b) (4) and the VAI classification for the inspection results of (b) (4), the application could be approved.

I concur with the conclusions reached by the chemistry reviewer and the CDRH reviewers regarding the acceptability of the manufacturing of the drug product, drug substance, and drug-device combination. Manufacturing site inspections were acceptable. Stability testing supports an expiry of the earlier date of either 27 months from the manufacturing date for the drug constituent component of Evzio or 24 months from the date of final assembly, packaging and labeling of Evzio. There are no outstanding issues.

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I concur with the review team that there are no outstanding CMC concerns that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

The following has been reproduced from page 10 of Dr. Hertz's review:

No new nonclinical studies were submitted in support of this application. There were no novel excipients and the specifications proposed for the drug substance impurities and drug product degradants all meet ICH Q3A(R2) and Q3B(R2) qualifications thresholds. There were no concerns based on the results of the extractable and leachable study. Recommendations for the product labeling were incorporated into the package insert, including the recommendation for Pregnancy Category B. As noted by Dr. Huynh, there is some inconsistency with the pregnancy category in package inserts for naloxone products, with some changed from Category B to C after 2001, without a rationale stated in reviews at the time. Dr. Huynh and his supervisor, Dr. Mellon, conclude that the change in category may reflect an error, and that available data suggest that Pregnancy Category B is more appropriate.

I concur with the review team that there are no outstanding pharmacology or toxicology issues that would preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the clinical pharmacology and biopharmaceutics data submitted in this application has been reproduced from pages 10 and 11 of Dr. Hertz's review:

Dr. Wei Qiu conducted the clinical pharmacology review. The Applicant conducted a randomized, 2-period cross-over study (Study IJ-900DV-03O) in 30 healthy subjects of a single injection of 0.4 mg naloxone HCl for injection administered using EVZIO NAI or the reference naloxone HCl using a standard syringe into the mid-anterolateral thigh. The Injection was either subcutaneous intramuscular based on the depth of fat under the skin and overlying the muscle, and the needle length. The needle length for EVZIO NAI is a nominal 0.5 inch and the needle length for the reference was 5/8 inch. The naloxone plasma concentration-time profiles are shown in Figure 1 from Dr. Qiu's review (p. 9).

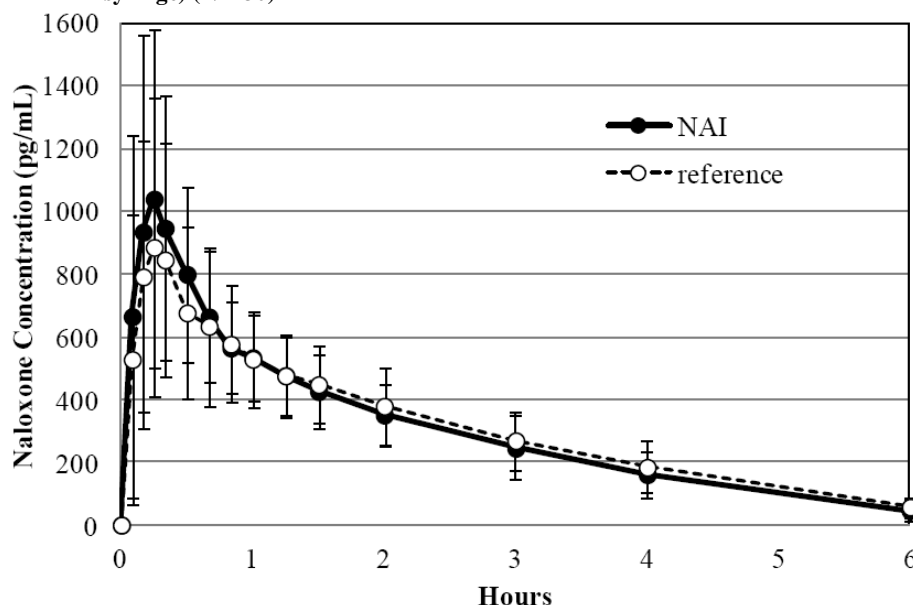
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Figure 1 Mean naloxone plasma concentration (ng/mL) time profiles following the administration of EVZIO NAI and Reference (0.4 mg injection via standard syringe) (N = 30)



The median T_{max} and half-life were similar for Evzio and the reference product (0.25 h vs. 0.33 h, and 1.28 h vs. 1.36 h). The AUC from the EVZIO injection was equivalent to the reference product (90% CIs of geometric mean ratios for naloxone AUC_t and AUC_{inf} within the bioequivalence limits of 80 to 125%). The C_{max} was 15% greater following EVZIO compared to the reference product (geometric mean 1.15, 90% CI [0.97, 1.37]).

Additional pertinent pharmacokinetic information is that following parenteral administration, naloxone hydrochloride is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation, and excreted in urine. Serum half-life in adults ranges from 30 to 81 minutes (mean 64 +/-12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 +/- 0.5 hours.

Inspections of the clinical and analytical portions of the comparative bioavailability study were conducted. No problems were identified and the data may be relied upon for Agency review.

I concur with the review team that there are no outstanding clinical pharmacology or biopharmaceutics concerns that would preclude approval of this application, and that the Applicant has provided data that demonstrate the bioequivalence of Evzio to naloxone.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

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7. Clinical/Statistical-Efficacy

No new efficacy data were submitted in support of this application.

8. Safety

The following summary of the clinical safety information submitted in this application has been reproduced from page 12 of Dr. Hertz's review:

There were no new safety studies submitted in support of this application. In the relative bioavailability study conducted in normal volunteers, dizziness, nausea, anosmia, dysgeusia, hyperhidrosis and hematoma were the only reported adverse event in subjects receiving Evzio. The comparator arm reported nausea, headache, injection site pain, and presyncope.

Naloxone is generally not administered outside of the setting of a suspected opioid overdose. Based on the adverse events reported in the labeling for Narcan, in the setting of an opioid-tolerant patient, administration of naloxone can result in precipitation of an acute withdrawal syndrome characterized by body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, and tachycardia. In the neonate, opioid withdrawal signs and symptoms also included: convulsions, excessive crying, and hyperactive reflexes.

Also as noted in the labelling for Narcan, in the postoperative setting, there have been post-marketing reports of hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation.

There is minimal to no risk from administration of a dose of 0.4 mg or 0.8 mg of naloxone to a person who has not had an opioid overdose if the person is not opioid tolerant. In the setting of a patient who is obtunded with respiratory depression, if the cause is not opioid overdose, no ill effect is expected, the instructions to seek emergency medical care are appropriate, and use of Evzio should not result in substantial delay in seeking that emergency care.

9. Advisory Committee Meeting

The application was not presented to an advisory committee as it is a simple reformulation of an approved drug that includes a new method of administration.

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10. Pediatrics

The following summary of the pediatric information in this application has been reproduced from pages 13 through 15 of Dr. Hertz's review:

Pediatric patients and children may be at risk for an opioid overdose as a result of several scenarios. Similar to adults, pediatric patients may receive an inadvertent overdose based on an error in dosing (too soon, too much), initiation of a concomitant drug that inhibits metabolism of the opioid, or cessation of a concomitant drug that had induced the metabolism of the opioid. In addition, children in a home where opioids are in use may come in contact with an opioid through improper storage or disposal, and become a patient in the setting of an overdose. Older children may experiment with opioid analgesics in an attempt to get high and inadvertently overdose. Therefore, pediatricians caring for pediatric patients prescribed opioids or caring for children who are otherwise well, but may be at risk for coming in contact with an opioid, may find it appropriate to prescribe naloxone for their patient or for children at risk for opioid contact, to be kept in the home as a safety precaution.

The package insert for Narcan includes pediatric labeling as follows:

USAGE IN CHILDREN

- Narcotic Overdose—Known or Suspected: The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone may be administered I.M. or S.C. in divided doses. If necessary, naloxone hydrochloride injection can be diluted with sterile water for injection.

This is in contrast to the following dosing regimen in adults:

USAGE IN ADULTS

- Narcotic Overdose—Known or Suspected: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of narcotic-induced or partial narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

The Applicant had discussed pursuing a waiver from pediatric studies under the Pediatric Research Equity Act based on there being only a small number of opioid overdoses in the pediatric population and a fixed-dose product was not suitable to accommodate weight-based dosing, that their product would not represent a meaningful benefit over currently approved products, and finally, that it was impossible or highly impracticable to conduct studies in pediatric patients.

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Regardless of the number of actual pediatric opioid overdoses, the number of children at risk is large based on the amount of opioid analgesics prescribed in the U.S., and the autoinjector configuration is intended to provide a benefit over the approved product that was only available in a vial for injection. However, not only are efficacy studies not feasible in pediatric patients in the same way they were not feasible in adults, even pharmacokinetic studies are not feasible because of limits regarding conducting studies in normal, healthy children. The Pediatric and Maternal Health Staff was contacted to assist with creating a path forward for pediatric populations. As noted in Dr. Wynn's review:

The following are off-label naloxone dosing recommendations, endorsed by the AAP [American Academy of Pediatrics] and the American Heart Association, for cardiopulmonary resuscitation and emergency cardiovascular care for full reversal of opioid effects:

- Younger than 5 years or body weight 20 kg or less: 0.1 mg/kg administered by IV push, intraosseous push, or by ET tube. Follow each dose given via ET tube with at least 5 mL of isotonic sodium chloride injection
- 5 years and older or body weight more than 20 kg: 2 mg administered by IV push, intraosseous push or by ET. Follow each dose given via ET with at least 5 mL of isotonic sodium chloride injection

However, weight-based dosing could result in a situation where it would be necessary to have multiple versions of the product on hand, and would risk a dose too low selected if an emergency arose.

Dr. Wynn expressed concern that the dose may be too low based on the recommendations of the AAP. However, limited data could be found in the Narcan application to support the pediatric dosing recommendations.

These questions were discussed further at a meeting of the Pediatric Research Committee on March 5, 2014. The dosing was considered adequate in the setting of use, the product was to be packaged with two doses so a second dose would be available, and as an initial treatment prior to the availability of emergency medical services. Another concern raised was that the needle could hit bone in the youngest patients as it was necessary to apply the autoinjector with some force. This could result in the needle breaking off or blockage of delivery of the drug. The Applicant cited the Center for Disease Control recommendation for a 7/8 inch needle for intramuscular vaccination in children ages 0 to 6 years, although this could result in over-penetration in 4% of children and the length of the exposed needle from Evzio is 0.5 inches. The following recommendations were made (from the meeting minutes dated March 20, 2014):

- The Division clarified that the intent of this product is to allow patients, caregivers, and guardians to administer this product when an intentional or unintentional opioid overdose is suspected. This product is being specifically developed to address the public health problems associated with widespread narcotic use/abuse.
- The PeRC discussed the risks of this product, which include failure to seek follow-up medical care, and breakage of the needle if it hits bone due to the needle length, and discussed whether the benefits outweigh the risks.

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- The PeRC concluded that it is reasonable to label the product now for all populations, but the Division should consider requiring the sponsor to conduct a safety study under FDAAA to ensure that the autoinjector can be used safely in the youngest population.
- The PeRC also recommended that labeling clearly describe safety concerns related to administration in small infants and children. The PeRC also agreed with the Division's plan to ensure that labeling clearly state that pediatric patients should seek medical care after administration of the product.

Language was added to the labeling with the instruction to pinch the thigh of pediatric patients less than one year of age to minimize the risk of striking bone. In addition, the Applicant agreed to commit to the following post-marketing safety requirement:

Conduct a study to demonstrate that the needle length is safe for use in patients less than one year of age during expected conditions of use.

11. Other Relevant Regulatory Issues

There were no unresolved regulatory issues associated with this application.

12. Labeling

The following comments regarding labeling have been reproduced from pages 15 and 16 of Dr. Hertz's review:

A proprietary name review by Dr. Borders-Hemphill found the proposed name Evzio acceptable.

Substantial changes were made to the package insert based on input from DMEPA, OPDP, SEALD, and DAAAP. While relying on the Agency's prior findings of safety and efficacy for Narcan, the Narcan package insert was not in the Physician Labeling Rule format, and contained language not consistent with current labeling efforts. First, the indication amended from language similar to Narcan as proposed by the Applicant:

(b) (4)

[Redacted text block]

The final agreed upon indication is based on the intended use of Evzio.

EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present.

EVZIO is not a substitute for emergency medical care.

Key elements of this indication are that Evzio is for use of known or suspected opioid overdose. In the community, the reason for a patient appearing obtunded with respiratory depression is unknown. If opioid overdose is a possibility, Evzio should be administered. Therefore, it is important that Evzio be obtained by patients in advance of a problem, acknowledging that unplanned overdose can occur with the use of opioids. This will also allow patients and their immediate caregiver, family or friends to have time to become familiar with the instructions for use and the trainer. Also critical is the need to continue to pursue emergency medical care as the duration of effect of naloxone is frequently shorter than the duration of effect of opioids.

Evzio will be packaged with two active units and one trainer. This way, if the initial response is less than expected or if the initial response wanes prior to the availability of emergency medical help, another dose can be given.

Recommendations for the carton and immediate container labels from DMEPA were conveyed to the Applicant and implemented. The immediate container label was considered the labeling on the outer case and on the device itself. Requests for change from DMEPA for the active device and the trainer were implemented. In particular, the purpose statement, “(b) (4)” was proposed by the Applicant for placement in several areas on the active device labeling. The Applicant agreed with a request to change this statement to “for use in opioid emergencies such as overdose” to help minimize the risk of failing to identify an appropriate opportunity to use Evzio based on confusion between what constitutes an opioid emergency and an opioid overdose.

The patient labeling for Evzio consists of a patient package insert, instructions for use for the trainer and for the active device. Extensive revisions were requested from OPDP and DMPP that were conveyed to the Applicant and accepted.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant has provided substantial evidence that supports the safety, efficacy and product quality of their naloxone autoinjector product, Evzio. This will be the first approved naloxone product specifically designed for ease of administration by non-medical individuals in the setting of an emergency. It has minimal to no known risks and can potentially save numerous lives, including those of pain or addiction patients who accidentally overdose, and those of small children, teenagers and others inadvertently or intentionally exposed to opioids in settings where these drugs are not adequately secured. The potentially enormous benefits of this product clearly outweigh the minimal risks that may be associated with its use in reversing opioid overdose. A key risk associated with the use of Evzio is that there may be a failure to obtain adequate medical follow-up, which is critical following initial overdose reversal. That risk has been appropriately addressed to the best of the Applicant's ability by the inclusion of visual and audio instructions for the person administering the drug; these instructions include noting the need to obtain emergency medical care immediately after administration of the naloxone. Another important safety consideration is the risk of precipitating withdrawal in opioid-dependent individuals. However, the risk of death from an overdose clearly outweighs risks that may be associated with precipitated withdrawal. Furthermore, the product labeling describes the importance of understanding that only people experiencing respiratory depression along with excessive sleepiness should receive the product.

- Postmarketing Risk Management Activities

None

- Postmarketing Study Requirements

To address the risk of a needle striking bone in infants, the Applicant has agreed to the following postmarketing safety requirement:

Conduct a study to demonstrate that the needle length is safe for use in patients less than one year of age during expected conditions of use.

NDA 205787

Evzio

Division Director's Review and Summary Basis for Approval

April 3, 2014

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

/s/

BOB A RAPPAPORT
04/02/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205787Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	CDTL Memo
NDA #/ Supplement #	205787/000
Applicant Name	Kaleo, Inc.
Date of Submission	December 20, 2013
PDUFA Goal Date	June 20, 2014
Proprietary Name / Established (USAN) Name	Evzio/ Naloxone Injection
Dosage Forms / Strength	0.4 mg, Injection
Proposed Indication(s)	<ul style="list-style-type: none"> • EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. • EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present. • EVZIO is not a substitute for emergency medical care.
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Steven Galati, MD, Josh Lloyd, MD
Pharmacology Toxicology Review	Carlic Huynh, PhD, R. Daniel Mellon, PhD
CMC Review/OBP Review	Ying Wang, PhD, Julia Pinto, PhD, Prasad Peri, PhD
ONDQA Microbiology Review	Jessica Cole, PhD, Bryan Riley, PhD
Clinical Pharmacology Review	Wei Qiu, PhD, Yun Xu, PhD
CDRH REGODB/DMQ/OC GHDB/ DAGID/ODE ODE/DAGRID	M. Isabel Tejero del Rio, MD, PhD; Carl Fischer, PhD Lana Shiu, M.D., Keith Marin, Keith Marin, QuynhNhu Nguyen, Ron Kaye,
OSI DBGC	Chase Bourke, PhD, Charles Bonapace, PharmD, William Taylor, PhD Juandria Williams,
OSE/DMEPA	Vicky Borders-Hemphill, PharmD, Morgan Walker, PharmD, Kellie Taylor, PharmD, MPH. Irene Chan, PharmD, BCPS
OND/SEALD	Abimbola Adebawale, Eric Brodsky, MD
OPDP/DCDP	L. Sheneé Toombs, Olga Salis, Michale Wade

OMP/DMPP	Karen Dowdy, RN, BSN, Sharon Mills, BSN, RN, CCRP, L. Shenee' Toombs, PharmD, Barbara Fuller, RN, MSN, CWOCN, LaShawn Griffiths, MSHS-PH, BSN, RN
Pediatric and Maternal Health Staff Review	Erica Wynn, MD, MPH, Hari Sachs, MD, Lynne Yao, MD.

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication ErrorsPrevention
 DSI=Division of Scientific Investigations
 OPDP=Office of Prescription Drug Promotion
 DCDP=Division of Consumer Drug Promotion
 OMP=Office of Medical Policy Initiatives
 DMPP=Division of Medical Policy Programs

Cross Discipline Team Leader Review

1. Introduction

Opioid overdose leading to death can occur in a variety of settings. Patients on opioid analgesics may inadvertently take too much trying to better manage pain, or through errors in dose or frequency. Initiating a new concomitant medication that inhibits the metabolic pathway of an opioid, or discontinuation of a concomitant medication that induces the metabolic pathway can result in overdose in a patient who has used their opioid analgesic according to instructions. Addition of a new medication with the adverse effect of central nervous system depression, or an error in judgment surrounding the use of alcohol can also create a situation of over sedation in a patient previously stable on an opioid. Overdose can occur in household contacts of a patient prescribed opioids by accident or through intentional misuse or abuse. Individuals abusing prescription opioid analgesics or illicit opioids can also inadvertently overdose. With the range of potency of available opioids, death from overdose can occur with the first attempt at abuse. Death due to overdose from most opioids may be preventable with the immediate administration of an opioid antagonist such as naloxone. However, there are limitations in the prevention of death in this setting. The effects of some opioids such as buprenorphine may be difficult to antagonize. Larger doses of antagonist may be necessary than are available and the opioid overdose must be reversed before hypoxia results in irreversible injury. Also, it is important to realize that the duration of antagonists such as naloxone are generally shorter than the duration of action of most opioids. Therefore, even when an antagonist is available, it is no substitute for seeking emergency medical help.

The use of naloxone for reversal of opioid overdose in the community has been increasing over the past decade through a number of public health initiatives generally centered around preventing overdose deaths in people who abuse opioids. As naloxone has only been available in vials for injection, these programs supply some combination of a vial or syringe of naloxone with a needle or nasal atomizer (an off-label route of administration). The subject of this NDA, Evzio, is a single-use, drug-device combination product, designed as an auto-injector intended for use in the community and is designed for use by non-medical people. The auto-injector design may also be appropriate for first responders.

2. Background

Naloxone HCl was first approved in 1971 (Narcan, NDA 016636), for intravenous, intramuscular, and subcutaneous administration. The current application is a 505(b)(2) application relying on the Agency's prior finding of the safety and efficacy for Narcan. As the marketing of Narcan has been discontinued, the Applicant used a generic product, International Medicinal System's naloxone HCl injection USP pre-filled syringe (ANDA 072076) for the relative bioavailability study necessary to create a scientific bridge to the

Agency's prior findings. The application was accepted for rolling review and was granted priority review status upon submission of the final sections reflecting the importance this product from the public health perspective. 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. While an off-label use, the bioavailability of commercial naloxone hydrochloride by the intranasal route of administration using a nasal atomizer may be less than the exposure following approved routes of administration, based on reports in the literature, but there are also reports in the literature and from addiction treatment programs that naloxone administered this way has been successful in reversing opioid overdose. Therefore, the smallest effective dose of naloxone that can be effective is unclear, and is likely dependent on a number of factors, including route of administration and the amount and type of opioid involved in the overdose. In discussion with the Applicant during development, it was not possible to design an efficacy study to define an effective range of naloxone use in the proposed setting. Pharmacodynamic measurements such as pupil dilation or response to inhaled carbon dioxide may demonstrate an effect of naloxone, but the relationships between experimental opioid effects and reversal of a clinically meaningful overdose are not defined. Administering enough opioid to actually create a clinically meaningful opioid overdose for this purpose is not ethical. Therefore, as a target for development of products for use in the community, the Agency has said that the pharmacokinetics of naloxone via an approved route must be matched, particularly, C_{max} and T_{max}. This type of study can be conducted in a normal healthy volunteer population without risk to the study participants. Note that in some of the excerpts from other reviews, Evzio is referred to as the naloxone autoinjector (NAI).

3. CMC/Device

Dr. Ying Wang performed the review of the drug substance and drug product. The information for the naloxone hydrochloride drug substance is referenced in DMF (b) (4) for which (b) (4) is the holder. According to Dr. Wang, the drug substance specifications mostly follow the USP and EP monographs and additional specifications for related substances meet the criteria in the ICH Q3A guideline. The drug product constituent component, 0.4 mg naloxone hydrochloride in an (b) (4) filled into a Type I (b) (4) glass cartridge, the primary container closure, (b) (4) the listed drug product (International Medicinal Systems, Naloxone HCl Injection, ANDA 072076) used for the relative bioavailability study. The only excipients are (b) (4) hydrochloric acid, and water. The drug product batches for the clinical study and registration stability lots meet the specifications and the specifications are acceptable.

The container closure system include the glass cartridge, a Type I (b) (4) gray (b) (4) rubber plunger which has contact with the drug solution, and an aluminum-crimping cap which does not have contact with the drug solution. The materials in contact with the drug solution comply with the USP and European Pharmacopoeia and are suitable for the storage of sterile drug product solution. An extractables study was completed with the rubber plungers and seals using a placebo of the drug product solution placebo (NaCl, pH 3.4) and isopropanol, as a control solvent. No significant peaks from the plunger or seals were observed.

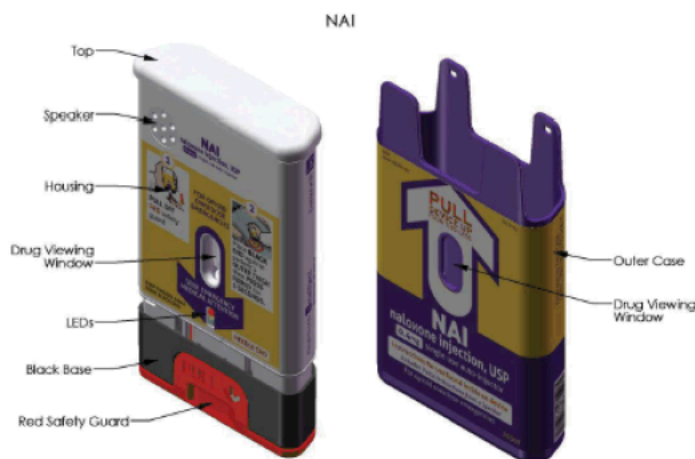
The drug product was stable during stability testing with relatively low impurity levels. The Applicant submitted 12 months of stability data under term storage conditions (25°C/60% RH), 6 months under intermediate storage conditions (30°C/65% RH), and 6 month accelerated storage condition (40°C/75% RH) are provided in the submission. The stability data support the proposed expiry of the earlier of either 27 months from the manufacturing date for the drug constituent component of EVZIO or 24 months from the date of final assembly, packaging, and labeling of EVZIO.

The drug constituent component manufacturing sites were all found to be acceptable by the CDER Office of Compliance.

The Applicant was granted a categorical exclusion for the environmental assessment based on the rationale that there would be a very low estimated concentration of drug substance at point of entry into the aquatic environment.

Dr. Jessica Cole conducted the product quality microbiology review. The drug is (b) (4) and filled into a glass cartridge. The filled glass cartridge is assembled with the needle and protective sheath. This cartridge assembly is (b) (4). Dr. Cole found the response to requested information adequate and the Applicant agreed to a request amendment to the specification for endotoxin to (b) (4) naloxone to prevent potential pyrogenic reactions in infants.

The CDRH engineering review was conducted by Dr. Lana Shiu. The device is a user-operated, (b) (4), needle-based system with audible and visual cues to guide the user through administration once the device is removed from its outer case. The drug cartridge container closure system for the naloxone drug product consists of a Type 1 (b) (4) glass cartridge with an (b) (4) plunger and an aluminum crimp cap lined with an (b) (4). When activated, the device injects a single dose of 0.4 mL (0.4 mg of naloxone HCl).



The total needle length is 5/8 of an inch and 1/2 of an inch that extends outside the device upon actuation. The needle is fully retracted into the device housing after use. (b) (4)

(b) (4). (b) (4) make contact with the drug product or injection site at any time.

(b) (4)

(b) (4)

As noted by Dr. Shiu (p. 4):

Under dosing is prevented (b) (4)

The Volume Dispensed is defined as a release specification to ensure dosing accuracy.

In addition, (b) (4). The activation, needle penetration, drug injection and retraction of the needle occur in less than five seconds, and of that time, the actual needle penetration and drug injection time is (b) (4) seconds. A red safety guard prevents accidental activation of the injection.

Also noted by Dr. Shiu (p.6):

(b) (4)

Intelliject (device developer for both NAI and EAI) relied on the prior validation study of EAI to support NAI development plan. CDRH provided the engineering device consult on the autoinjector and its software during the review of EAI (epiCard) during the IND 76367 as well as during the NDA 201739.

Device design, materials of construction, biocompatibility, sterilization, and shelf-life expectancy are consistent with that of IND 76367/NDA201739.

Per FDA's 2005 Guidance: *Medical Devices with Sharps Injury Prevention Features*, 500 NAI devices were tested *in-vitro* to confirm needle retraction. All 500 devices passed needle retraction testing, further verifying the NAI retractable needle feature as described in report IJ-731R-03O.

Dr. Shiu concluded that safety and efficacy have been demonstrated in this device.

The CDRH Human Factors and Device Use review was conducted by Ms. Quynh Nhu Nguyen. Preliminary and formative studies were conducted to optimize labeling, instructions for use and device design user interface. A human factors validation study was conducted with 40 participants, consisting of 19 juveniles and 21 adults, asked to deliver a simulated injection without training. Ms. Nguyen noted the following (p. 4):

The following sections provide a discussion on the observed use errors and difficulties which included the four issues identified above:

- Five juvenile participants used the trainer instead of study device but post-test user interview showed that these participants confirmed that they knew which device was which, and stated that they used the trainer intentionally because the simulation as a test or pretend situation.
- Four juvenile participants experienced difficulty with pulling off red safety guard. Intelliject confirmed that all adult participants could remove the red safety guard, and four juvenile participants experienced some difficulty initially but were able to pull it off.
- Four adult participants and two juvenile participants did not inject into the outer thigh but instead, they injected into the front or back of the thigh, inner thigh, etc. Intelliject confirmed that NAI is indicated for subcutaneous or intramuscular administration. While Intelliject has determined that the outer thigh is the ideal injection site location, if NAI were to be administered into the thigh, legs or upper arms/shoulder, they stated that the patient would still receive a SC or IM injection.
- Two participants (one adult and one juvenile) did not press device firmly against the skin for device activation. Based on post-test interview responses, Intelliject

considered changes to the voice script to emphasize the need to push harder, and to wait until a click is heard. However, Intelliject believes that if a user commits a critical use error, the residual risk is that the patient would be receiving the current standard of care from paramedic and EMT personnel.

- Two juvenile participants did not hold the device in place for at least 1 second. Intelliject confirmed that the injection time of the needle and dispensing time of the drug is less than (b) (4) seconds. In addition, the voice prompt provides a device count down “five, four, three, two, one” after the injection is initiated.

Ms. Nguyen concluded that the results of the human factors study were acceptable, and no further optimization on the design and/or labeling was necessary.

The CDRH Office of Compliance review was conducted by Dr. Isabel Tejero del Rio. A number of deficiencies were identified and submitted to the Applicant following her initial review dated January 21, 2014. In a memo dated February 18, 2014, Dr. Tejero noted that the Applicant’s response to the deficiency letter dated January 22, 2014, was adequate with no residual deficiencies. Two facilities were identified as being subject to applicable Medical Device Regulations under 21 CFR Part 820. One site, Kaléo Inc., had an inspection on June 27, 2011, that was classified no action indicated (NAI). The second site, (b) (4)

Therefore, (b) (4), although an inspection under the Medical Device regulation on (b) (4), was classified NAI, a recommendation was made for a pre-approval inspection for compliance with 21 CFR Part 820. Dr. Tejero did note the following (p. 4):

However, CDRH/OC would consider acceptable a post-market inspection of the (b) (4) facility due to the public health benefit of the rapid approval of Evzio naloxone autoinjector, and based on the adequate desk review and previous NAI inspections of two (b) (4)

A form FDA-483 was issued for the (b) (4) site with three observations. The first observation was that the firm was (b) (4)

The Applicant responded that they were awaiting the final labeling from FDA prior to completing (b) (4). The required documentation to complete a desk review of the (b) (4) assembly line and investigators were able to observe the line in action and found no deficiencies.

The next two observations were:

OBSERVATION 2: Process control procedures that describe any process controls necessary to ensure conformance to specifications have not been adequately established. Specifically:

A. The firm is not currently (b) (4) in that they have not completed the performance qualification for (b) (4)

Qualification of the controlled environment areas is required before the firm may proceed with the commercial scale process performance qualification (PPQ) batches.

B. The equipment qualification protocol, (b) (4)

Evaluation: The investigator stated during the March 21st call that the firm (b) (4)

The investigator indicated that she did not have any major concerns respect to the qualification process. Furthermore, the investigator believed that the (b) (4) could be completed within a week, as indicated by the firm.

OBSERVATION 3: Procedures for corrective and preventive action have not been adequately established. Specifically,

(b) (4)

Evaluation: the investigator stated during the phone call of March 21st that this observation had been corrected before they closed the inspection. Thus, CDRH/OC has no additional concerns regarding the issue.

Dr. Tejero concluded that, based on the nature of the observations cited in form FDA-483, in conjunction with discussions with the investigators, district office, the CDER Office of Compliance and the CDRH Office of Compliance, the inspection was classified Voluntary Action Indicated and that in conjunction with a satisfactory desk review of the NDA, adequate inspectional history of (b) (4) and the VAI classification for the inspection results of (b) (4), the application could be approved.

I concur with the conclusions reached by the chemistry reviewer and the CDRH reviewers regarding the acceptability of the manufacturing of the drug product, drug substance, and drug-

device combination. Manufacturing site inspections were acceptable. Stability testing supports an expiry of the earlier date of either 27 months from the manufacturing date for the drug constituent component of Evzio or 24 months from the date of final assembly, packaging and labeling of Evzio. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

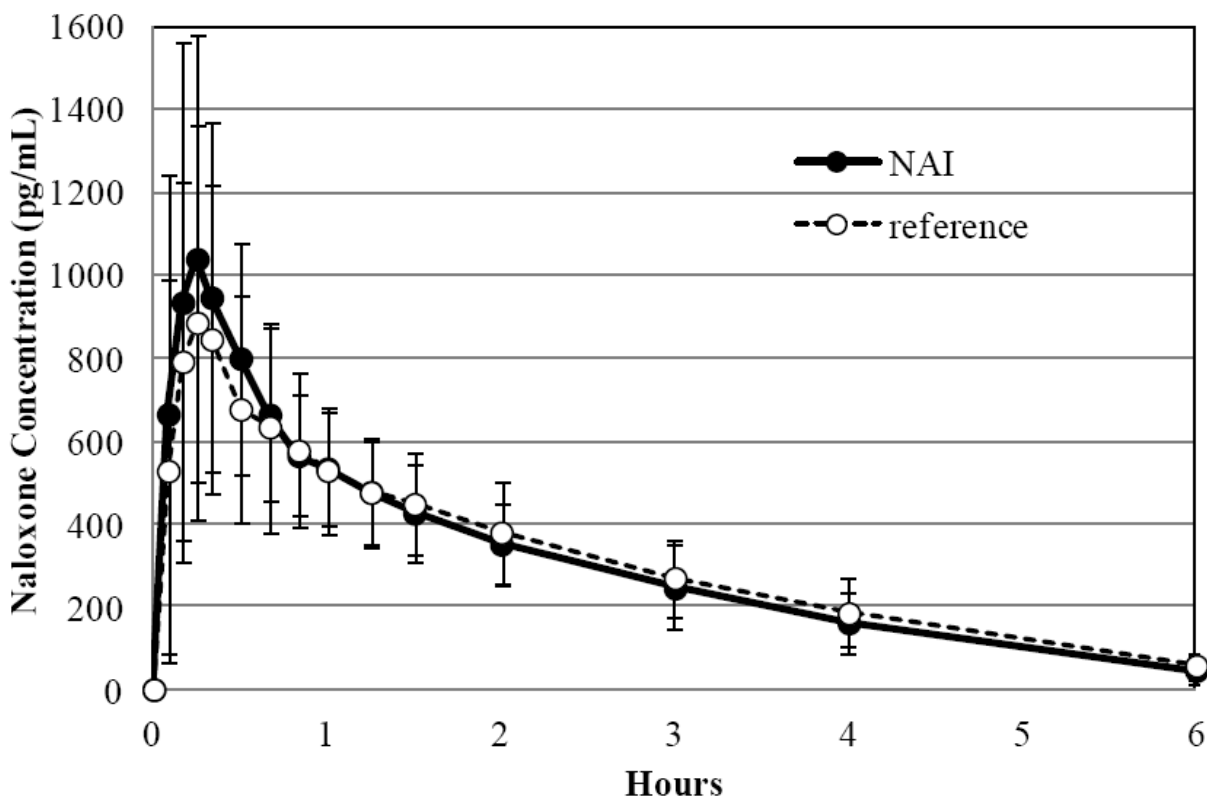
No new nonclinical studies were submitted in support of this application. There were no novel excipients and the specifications proposed for the drug substance impurities and drug product degradants all meet ICH Q3A(R2) and Q3B(R2) qualification thresholds. There were no concerns based on the results of the extractable and leachable study. Recommendations for the product labeling were incorporated into the package insert, including the recommendation for Pregnancy Category B. As noted by Dr. Huynh, there is some inconsistency with the pregnancy category in package inserts for naloxone products, with some changed from Category B to C after 2001, without a rationale stated in reviews at the time. Dr. Huynh and his supervisor, Dr. Mellon, conclude that the change in category may reflect an error, and that available data suggest that Pregnancy Category B is more appropriate.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology or toxicology issues that preclude approval.

5. Clinical Pharmacology

Dr. Wei Qiu conducted the clinical pharmacology review. The Applicant conducted a randomized, 2-period cross-over study (Study IJ-900DV-03O) in 30 healthy subjects of a single injection of 0.4 mg naloxone HCl for injection administered using Evzio or the reference naloxone HCl using a standard syringe into the mid-anterolateral thigh. The injection was either subcutaneous or intramuscular based on the depth of fat under the skin and overlying the muscle and the needle length. The effective needle length of Evzio is 0.5 inch and the needle length for the reference was 5/8 of an inch. The naloxone plasma concentration-time profiles are shown in Figure 1 from Dr. Qiu's review (p. 9).

Figure 1 Mean naloxone plasma concentration (ng/mL) time profiles following the administration of EVZIO NAI and Reference (0.4 mg injection via standard syringe) (N = 30)



The median T_{max} and half-life were similar for Evzio and the reference product (0.25 h vs. 0.33 h, and 1.28 h vs. 1.36 h). The AUC from the Evzio injection was within the bioequivalence limits of 80 to 125% as compared to the reference product (90% CIs of geometric mean ratios for naloxone AUC_t and AUC_{inf}). The C_{max} was 15% greater following administration of Evzio compared to the reference product (geometric mean 1.15, 90% CI [0.97, 1.37]).

Additional pertinent pharmacokinetic information is that following parenteral administration, naloxone hydrochloride is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation, and excreted in urine. Serum half-life in adults ranges from 30 to 81 minutes (mean 64 +/- 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 +/- 0.5 hours.

Inspections of the clinical and analytical portions of the comparative bioavailability study were conducted. No problems were identified and the data may be relied upon for Agency review.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not Applicable.

7. Clinical/Statistical-Efficacy

No new clinical efficacy studies were submitted in support of this application. The Applicant is relying on the Agency's prior findings of efficacy and safety for Narcan (naloxone hydrochloride), NDA 016636.

8. Safety

There were no new safety studies submitted in support of this application. In the relative bioavailability study conducted in normal volunteers, dizziness, nausea, anosmia, dysgeusia, hyperhidrosis and hematoma were the only reported adverse events in subjects receiving Evzio. The comparator arm reported nausea, headache, injection site pain, and presyncope.

Naloxone is generally not administered outside of the setting of a suspected opioid overdose. Based on the adverse events reported in the labeling for Narcan, in the setting of an opioid-tolerant patient, administration of naloxone can result in precipitation of an acute withdrawal syndrome characterized by body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, and tachycardia. In the neonate, opioid withdrawal signs and symptoms also included: convulsions, excessive crying, and hyperactive reflexes.

Also as noted in the labelling for Narcan, in the postoperative setting, there have been post-marketing reports of hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation.

There is minimal to no risk from administration of a dose of 0.4 mg or 0.8 mg of naloxone to a person who has not had an opioid overdose if the person is not opioid-tolerant. In the setting of a patient who is obtunded with respiratory depression, if the cause is not opioid overdose, no ill effect is expected, the instructions to seek emergency medical care are appropriate, and use of Evzio should not result in substantial delay in seeking that emergency care.

9. Advisory Committee Meeting

This application was not taken to an advisory committee meeting. There were no issues that arose during the review period requiring external advice.

10. Pediatrics

Pediatric patients and children may be at risk for an opioid overdose as a result of several scenarios. Similar to adults, pediatric patients may receive an inadvertent overdose based on an error in dosing (too soon, too much), initiation of a concomitant drug that inhibits metabolism of the opioid, or cessation of a concomitant drug that had induced the metabolism of the opioid. In addition, children in a home where opioids are in use may come in contact with an opioid through improper storage or disposal, and become a patient in the setting of an overdose. Older children may experiment with opioid analgesics in an attempt to get high and inadvertently overdose. Therefore, pediatricians caring for pediatric patients prescribed opioids or caring for children who are otherwise well, but may be at risk for coming in contact with an opioid, may find it appropriate to prescribe naloxone for their patient or for children at risk for opioid contact, to be kept in the home as a safety precaution.

The package insert for Narcan includes pediatric labeling as follows:

USAGE IN CHILDREN

- Narcotic Overdose—Known or Suspected: The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone may be administered I.M. or S.C. in divided doses. If necessary, naloxone hydrochloride injection can be diluted with sterile water for injection.

This is in contrast to the following dosing regimen in adults:

USAGE IN ADULTS

- Narcotic Overdose—Known or Suspected: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of narcotic-induced or partial narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

The Applicant had discussed pursuing a waiver from pediatric studies under the Pediatric Research Equity Act based on there being only a small number of opioid overdoses in the pediatric population and a fixed-dose product was not suitable to accommodate weight-based dosing, that their product would not represent a meaningful benefit over currently approved products, and finally, that it was impossible or highly impracticable to conduct studies in pediatric patients.

Regardless of the number of actual pediatric opioid overdoses, the number of children at risk is large based on the amount of opioid analgesics prescribed in the U.S., and the autoinjector configuration is intended to provide a benefit over the approved product that was only available in a vial for injection. However, not only are efficacy studies not feasible in pediatric

patients in the same way they were not feasible in adults, even pharmacokinetic studies are not feasible because of limits regarding conducting studies in normal, healthy children. The Pediatric and Maternal Health Staff was contacted to assist with creating a path forward for pediatric populations. As noted in Dr. Wynn's review:

The following are off-label naloxone dosing recommendations, endorsed by the AAP [American Academy of Pediatrics] and the American Heart Association, for cardiopulmonary resuscitation and emergency cardiovascular care for full reversal of opioid effects:

- Younger than 5 years or body weight 20 kg or less: 0.1 mg/kg administered by IV push, intraosseous push, or by ET tube. Follow each dose given via ET tube with at least 5 mL of isotonic sodium chloride injection
- 5 years and older or body weight more than 20 kg: 2 mg administered by IV push, intraosseous push or by ET. Follow each dose given via ET with at least 5 mL of isotonic sodium chloride injection

However, weight-based dosing could result in a situation where it would be necessary to have multiple versions of the product on hand, and would risk a dose too low selected if an emergency arose.

Dr. Wynn expressed concern that the dose may be too low based on the recommendations of the AAP. However, limited data could be found in the Narcan application to support the pediatric dosing recommendations.

These questions were discussed further at a meeting of the Pediatric Research Committee on March 5, 2014. The dosing was considered adequate in the setting of use, the product was to be packaged with two doses so a second dose would be available, and as an initial treatment prior to the availability of emergency medical services. Another concern raised was that the needle could hit bone in the youngest patients as it was necessary to apply the autoinjector with some force. This could result in the needle breaking off or blockage of delivery of the drug. The Applicant cited the Center for Disease Control recommendation for a 7/8 inch needle for intramuscular vaccination in children ages 0 to 6 years, although this could result in over-penetration in 4% of children and the length of the exposed needle from Evzio is 0.5 inches. The following recommendations were made (from the meeting minutes dated March 20, 2014):

- The Division clarified that the intent of this product is to allow patients, caregivers, and guardians to administer this product when an intentional or unintentional opioid overdose is suspected. This product is being specifically developed to address the public health problems associated with widespread narcotic use/abuse.
- The PeRC discussed the risks of this product, which include failure to seek follow-up medical care, and breakage of the needle if it hits bone due to the needle length, and discussed whether the benefits outweigh the risks.
- The PeRC concluded that it is reasonable to label the product now for all populations, but the Division should consider requiring the sponsor to conduct a safety study under FDAAA to ensure that the autoinjector can be used safely in the youngest population.

- The PeRC also recommended that labeling clearly describe safety concerns related to administration in small infants and children. The PeRC also agreed with the Division's plan to ensure that labeling clearly state that pediatric patients should seek medical care after administration of the product.

Language was added to the labeling with the instruction to pinch the thigh of pediatric patients less than one year of age to minimize the risk of striking bone. In addition, the Applicant agreed to commit to the following post-marketing safety requirement:

Conduct a study to demonstrate that the needle length is safe for use in patients less than one year of age during expected conditions of use.

11. Other Relevant Regulatory Issues

A review of the financial disclosure information by Dr. Galati revealed no irregularities.

There are no other unresolved relevant regulatory issues.

12. Labeling

A proprietary name review by Dr. Borders-Hemphill found the proposed name Evzio acceptable.

Substantial changes were made to the package insert based on input from DMEPA, OPDP, SEALD, and DAAAP. While relying on the Agency's prior findings of safety and efficacy for Narcan, the Narcan package insert was not in the Physician Labeling Rule format, and contained language not consistent with current labeling efforts. First, the indication amended from language similar to Narcan as proposed by the Applicant:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

The final agreed upon indication is based on the intended use of Evzio.

EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present.

EVZIO is not a substitute for emergency medical care.

Key elements of this indication are that Evzio is for use of known or suspected opioid overdose. In the community, the reason for a patient appearing obtunded with respiratory depression is unknown. If opioid overdose is a possibility, Evzio should be administered. Therefore, it is important that Evzio be obtained by patients in advance of a problem, acknowledging that unplanned overdose can occur with the use of opioids. This will also allow patients and their immediate caregiver, family or friends to have time to become familiar with the instructions for use and the trainer. Also critical is the need to continue to pursue emergency medical care as the duration of effect of naloxone is frequently shorter than the duration of effect of opioids.

Evzio will be packaged with two active units and one trainer. This way, if the initial response is less than expected or if the initial response wanes prior to the availability of emergency medical help, another dose can be given.

Recommendations for the carton and immediate container labels from DMEPA were conveyed to the Applicant and implemented. The immediate container label was considered the labeling on the outer case and on the device itself. Requests for change from DMEPA for the active device and the trainer were implemented. In particular, the purpose statement, “(b) (4)” was proposed by the Applicant for placement in several areas on the active device labeling. The Applicant agreed with a request to change this statement to “for use in opioid emergencies such as overdose” to help minimize the risk of failing to identify an appropriate opportunity to use Evzio based on confusion between what constitutes (b) (4) and an opioid overdose.

The patient labeling for Evzio consists of a patient package insert, instructions for use for the trainer and for the active device. Extensive revisions were requested from OPDP and DMPP that were conveyed to the Applicant and accepted.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - approval
- Risk Benefit Assessment

There is little risk associated with the administration of naloxone to a person who does not need it. There are grave consequences for failing to administer naloxone soon after an opioid overdose. Evzio offers the first configuration of naloxone intended for use in the community setting where the person administering the

product is not a medically trained individual or first responder. Ideally, this type of product will be prescribed for patients using opioids, and even for anyone else at risk for opioid overdose in settings where opioids are available, such as others in opioid-containing households who may accidentally or intentionally ingest or come in contact with opioids. It will also be useful where opioids are available in the setting of known abuse.

- Recommendation for Postmarketing Risk Management Activities
None.
- Recommendation for other Postmarketing Study Commitments

To address the risk of a needle striking bone, the Applicant has agreed to the following postmarketing safety requirement:

Conduct a study to demonstrate that the needle length is safe for use in patients less than one year of age during expected conditions of use.

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

/s/

SHARON H HERTZ
04/01/2014

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EVZIO safely and effectively. See full prescribing information for EVZIO.

EVZIO (naloxone hydrochloride injection) Auto-Injector for intramuscular or subcutaneous use

Initial U.S. Approval: 1971

INDICATIONS AND USAGE

EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. (1)

EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present. (1)

EVZIO is not a substitute for emergency medical care. (1)

DOSAGE AND ADMINISTRATION

- EVZIO is for intramuscular or subcutaneous use only. (2.1)
- Seek emergency medical care immediately after use. (2.1)
- Administer EVZIO to adult or pediatric patients into the anterolateral aspect of the thigh, through clothing if necessary. (2.2)
- Additional doses may be administered every 2 to 3 minutes until emergency medical assistance arrives. (2.2)
- In pediatric patients under the age of one, the caregiver should pinch the thigh muscle while administering the dose. (2.2)
- **If the electronic voice instruction system does not operate properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions on the flat surface of its label. (2.1)**

DOSAGE FORMS AND STRENGTHS

Injection: 0.4 mg/0.4 mL naloxone hydrochloride solution in a pre-filled auto-injector. (3)

CONTRAINDICATIONS

Patients known to be hypersensitive to naloxone hydrochloride (4)

WARNINGS AND PRECAUTIONS

- Due to the duration of action, keep the patient under continued surveillance and repeated doses of naloxone should be administered, as necessary, while awaiting emergency medical assistance. (5.1)
- Other supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance. (5.1)
- Reversal of respiratory depression by partial agonists or mixed agonists/antagonists such as buprenorphine and pentazocine, may be incomplete. (5.2)
- Use in patients who are opioid dependent may precipitate acute abstinence syndrome. (5.3)
- Patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects should be monitored in an appropriate healthcare setting (5.3)
- In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. (5.3)

ADVERSE REACTIONS

The following adverse reactions have been identified during use of naloxone hydrochloride in the post-operative setting: Hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation. (6)

Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated signs and symptoms of opioid withdrawal including: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal signs and symptoms also included: convulsions, excessive crying, hyperactive reflexes. (6)

To report SUSPECTED ADVERSE REACTIONS, contact kaleo, Inc. at 1-855-773-8946 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 4/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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2 DOSAGE AND ADMINISTRATION

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3 DOSAGE FORMS AND STRENGTHS

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present.

EVZIO is not a substitute for emergency medical care.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- EVZIO is for intramuscular and subcutaneous use only.
- Because treatment of suspected opioid overdose must be performed by someone other than the patient, instruct the prescription recipient to inform those around them about the presence of EVZIO and the *Instructions for Use*.
- Seek emergency medical care immediately after use. Since the duration of action of most opioids exceeds that of naloxone hydrochloride, and the suspected opioid overdose may occur outside of supervised medical settings, seek immediate emergency medical assistance, keep the patient under continued surveillance, and administer repeated doses of EVZIO as necessary. Always seek emergency medical assistance in the event of a suspected, potentially life-threatening opioid emergency after administration of the first dose of EVZIO.
- Additional doses of EVZIO may be required until emergency medical assistance becomes available.
- Do not attempt to reuse EVZIO. Each EVZIO contains a single dose of naloxone.
- Visually inspect EVZIO through the viewing window for particulate matter and discoloration prior to administration. Do not administer unless the solution is clear and the glass container is undamaged.

The *Instructions for Use* should be read by the patient or caregiver at the time they receive a prescription for EVZIO. Provide the following instructions to the patient or caregiver:

- EVZIO must be administered according to the printed instructions on the device label or the electronic voice instructions (EVZIO contains a speaker that provides voice instructions to guide the user through each step of the injection). **If the EVZIO electronic voice instruction system does not operate properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions on its label.**
- Once the red safety guard is removed, EVZIO must be used immediately or disposed of properly. Do not attempt to replace the red safety guard once it is removed.

Upon actuation, EVZIO automatically inserts the needle intramuscularly or subcutaneously, delivers 0.4 mg naloxone hydrochloride injection, and retracts the needle fully into its housing. Post injection,

the black base locks in place, a red indicator appears in the viewing window, and electronic visual and audible instructions signal that EVZIO has delivered the intended dose of naloxone hydrochloride and instructs the user to seek emergency medical attention.

2.2 Dosing Information

Administer the initial dose of EVZIO to adult or pediatric patients intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary, and seek emergency medical assistance. Administer EVZIO as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death. The requirement for repeat doses of EVZIO depends upon the amount, type, and route of administration of the opioid being antagonized.

If the desired response is not obtained after 2 or 3 minutes, another EVZIO dose may be administered. If there is still no response and additional doses are available, additional EVZIO doses may be administered every 2 to 3 minutes until emergency medical assistance arrives. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete or require higher doses of naloxone.

Dosing in Adults and Pediatric Patients over Age One

Instruct patients or their caregivers to administer EVZIO according to the *Instructions for Use*, intramuscularly or subcutaneously.

Dosing in Pediatric Patients under Age One

In pediatric patients under the age of one, the caregiver should pinch the thigh muscle while administering EVZIO.

3 DOSAGE FORMS AND STRENGTHS

Injection: 0.4 mg/0.4 mL naloxone hydrochloride solution in a pre-filled auto-injector. Each EVZIO delivers 0.4 mg naloxone hydrochloride injection (0.4 mL).

4 CONTRAINDICATIONS

EVZIO is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Duration of Effect

The duration of action of most opioids is likely to exceed that of EVZIO resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms. Therefore, it is necessary to seek immediate emergency medical assistance after delivering the first dose of EVZIO, keep the patient under continued surveillance, and repeat doses of EVZIO as

necessary. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

5.2 Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine, may be incomplete. Large doses of naloxone hydrochloride are required to antagonize buprenorphine because the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

5.3 Precipitation of Severe Opioid Withdrawal

The use of EVZIO in patients who are opioid dependent may precipitate an acute abstinence syndrome 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. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes.

Abrupt postoperative reversal of opioid depression after using naloxone hydrochloride may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, after use of naloxone hydrochloride, patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects should be monitored for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in an appropriate healthcare setting. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Duration of effect [*see Warnings and Precautions (5.1)*]
- Precipitation of Severe Opioid Withdrawal [*see Warnings and Precautions (5.3)*]

The following adverse reactions have been identified during post-approval use of naloxone hydrochloride in the post-operative setting. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a

causal relationship to drug exposure: Hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation [*see Warnings and Precautions (5.3)*].

Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated an acute withdrawal syndrome. Signs and symptoms have included: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal signs and symptoms also included: convulsions, excessive crying, hyperactive reflexes [*see Warnings and Precautions (5.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well-controlled studies with EVZIO in pregnant women. Animal studies were conducted with naloxone hydrochloride given during organogenesis in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day. These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride. Because animal reproduction studies are not always predictive of human response, EVZIO should be used during pregnancy only if clearly needed.

Clinical Considerations

Naloxone hydrochloride crosses the placenta, and may precipitate withdrawal in the fetus as well as in the opioid-dependent mother. The fetus should be evaluated for signs of distress after EVZIO is used. Careful monitoring is needed until the fetus and mother are stabilized.

Data

Animal Data

Naloxone hydrochloride was administered during organogenesis to mice and rats at doses 4-times and 8-times, respectively, the dose of 10 mg/day given to a 50 kg human (when based on body surface area or mg/m²). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.

8.3 Nursing Mothers

It is not known whether naloxone hydrochloride is present in human milk. Because many drugs are present in human milk, exercise caution when EVZIO is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of EVZIO (for intramuscular and subcutaneous use) have been established in pediatric patients for known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Use of naloxone hydrochloride in pediatric patients is supported by evidence from adequate and well-controlled studies of naloxone hydrochloride in adults with additional data from 15 clinical studies (controlled and uncontrolled) in which neonates and pediatric patients received parenteral naloxone in doses ranging from 0.005 mg/kg to 0.01 mg/kg. Safety and effectiveness are also supported by use of other naloxone hydrochloride products in the post-marketing setting as well as data available in the medical literature and clinical practice guidelines.

Absorption of naloxone hydrochloride following subcutaneous or intramuscular administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds dramatically to naloxone hydrochloride injection, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized. In opioid-dependent pediatric patients, (including neonates), administration of naloxone may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts [*see Warnings and Precautions (5.3)*].

In neonates and pediatric patients less than 1 year of age, careful observation of the administration site for evidence of residual needle parts and/or signs of infection is warranted [*see Dosage and Administration (2.1)*].

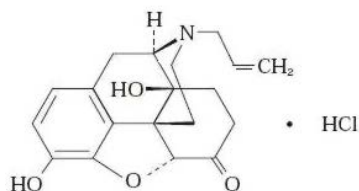
8.5 Geriatric Use

Geriatric patients have a greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Therefore, the systemic exposure of naloxone can be higher in these patients.

Clinical studies of naloxone hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11 DESCRIPTION

EVZIO (naloxone hydrochloride injection, USP) is a pre-filled, single-use auto-injector. EVZIO is not made with natural rubber latex. Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following structure:



$C_{19}H_{21}NO_4 \cdot HCl$

M.W. 363.84

Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Each 0.4 mL in EVZIO contains inactive ingredients of 3.34 mg of sodium chloride, hydrochloric acid to adjust pH, and water for injection. The pH range is 3.0 to 4.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation, and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

12.2 Pharmacodynamics

When naloxone hydrochloride is administered intravenously, the onset of action is generally apparent within two minutes. The time to onset of action is shorter for intravenous compared to subcutaneous or intramuscular routes of administration.

The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride.

12.3 Pharmacokinetics

In one pharmacokinetic study in 30 healthy subjects, a single 0.4 mg subcutaneous or intramuscular naloxone injection administered using EVZIO provides equivalent naloxone AUC and 15% greater naloxone C_{max} in comparison to a single 0.4 mg subcutaneous or intramuscular naloxone injection administered using a standard syringe.

Following a single EVZIO injection, the median T_{max} of naloxone was reached at 15 minutes (range 5 minutes to 1.2 hours), with a mean (± SD) C_{max} value of 1.24 (± 0.64) ng/mL. The mean (± SD) plasma half-life of naloxone in healthy adults was 1.28 (± 0.48) hours. In the same study, following administration of a single dose of 0.4 mg naloxone injection using a standard syringe, the median T_{max} was 20 minutes (range 5 minutes to 2.03 hours) and the mean (± SD) C_{max} value was 1.07 (± 0.48) ng/mL. The mean (± SD) plasma half-life was 1.36 (± 0.32) hours.

Distribution

Following parenteral administration, naloxone is distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

Metabolism

Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucuronide as the major metabolite.

Elimination

After an oral or intravenous dose, about 25-40% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours. Following a single EVZIO injection, the mean (\pm SD) plasma half-life of naloxone in healthy adults was 1.28 (\pm 0.48) hours. In a neonatal study of naloxone injection, the mean (\pm SD) plasma half-life was observed to be 3.1 (\pm 0.5) hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.

Impairment of Fertility

Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no adverse effect of naloxone hydrochloride on fertility.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Carton containing two EVZIO (naloxone hydrochloride injection, USP) 0.4 mg auto-injectors and a single Trainer for EVZIO - NDC 60842-030-01

16.2 Storage and Handling

Store EVZIO in the outer case provided.

Store at controlled room temperature 15°C to 25°C (59°F to 77°F) excursions permitted between 4°C and 40°C (between 39°F and 104°F).

Before using, check to make sure the solution in the auto-injector is not discolored. Replace EVZIO if the solution is discolored or contains a precipitate.

17 PATIENT COUNSELING INFORMATION

Advise the patient and family members or caregivers to read the FDA-approved patient labeling (*Instructions for Use*).

Instruct patients and their family members or caregivers to:

- Become familiar with the following information contained in the carton as soon as they receive EVZIO:
 - EVZIO Instructions for Use
 - Trainer for EVZIO Instructions for Use
 - Trainer for EVZIO
- Practice using the Trainer before EVZIO is needed.
 - Each EVZIO (which is purple and yellow) can only be used one time; however, the Trainer (which is black and white) can be re-used for training purposes and its red safety guard can be removed and replaced.
 - Both EVZIO and the Trainer for EVZIO incorporate the electronic voice instruction system.
- Make sure EVZIO is present whenever persons may be intentionally or accidentally exposed to an opioid to treat serious opioid overdose (i.e., opioid emergencies).

Instruct the patients and their family members or caregivers how to recognize the signs and symptoms of an opioid overdose requiring the use of EVZIO such as the following:

- Extreme sleepiness - inability to awaken a patient verbally or upon a firm sternal rub.
- Breathing problems - this can range from slow or shallow breathing to no breathing in a patient who cannot be awakened.
- Other signs and symptoms that may accompany sleepiness and breathing problems include the following:
 - Extremely small pupils (the black circle in the center of the colored part of the eye) sometimes called “pinpoint pupils.”
 - Slow heartbeat and/or low blood pressure.

Instruct them that when in doubt, if a patient is unresponsive, and an opioid overdose is suspected, administer EVZIO as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death. Instruct them to seek emergency medical assistance after administering the first dose of EVZIO.

Duration of Effect

Instruct patients and their family members or caregivers that since the duration of action of most opioids may exceed that of naloxone, seek immediate emergency medical assistance, keep the patient under continued surveillance, and administer repeated doses of EVZIO as necessary.

Limited Efficacy for/with Partial Agonists or Mixed Agonist/Antagonists

Instruct patients and their family members or caregivers that the reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine, may be incomplete.

Precipitation of Severe Opioid Withdrawal

Instruct patients and their family members or caregivers that the use of EVZIO in patients who are opioid dependent may precipitate an acute abstinence syndrome 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. In neonates, opioid withdrawal may be life threatening if not recognized and properly treated, and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes.

Administration Instructions

Instruct patients and their family members or caregivers about the following important information:

- EVZIO is user actuated and may be administered through clothing [e.g., pants, jeans, etc.] if necessary.
 - Inject EVZIO while pressing into the anterolateral aspect of the thigh. In pediatric patients less than 1 year of age, pinch the thigh muscle while administering EVZIO.
 - Upon actuation, EVZIO automatically inserts the needle intramuscularly or subcutaneously, delivers the naloxone, and retracts the needle fully into its housing. The needle is not visible before, during, or after injection.
 - Each EVZIO can only be used one time.
 - If the electronic voice instruction system on EVZIO does not work properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions on its label.
 - The electronic voice instructions are independent of activating EVZIO and are not required to wait for the voice instructions to be completed prior to moving to the next step in the injection process.
 - Post-injection, the black base locks in place, a red indicator appears in the viewing window and electronic visual and audible instructions signal that EVZIO has delivered the intended dose of naloxone hydrochloride.
 - EVZIO's red safety guard should not be replaced under any circumstances. However, the Trainer is designed for re-use and its red safety guard can be removed and replaced.
 - It is recommended that patients and caregivers become familiar with the training device provided and read the *Instructions for Use*; however, untrained caregivers or family members should still attempt to use EVZIO during a suspected opioid overdose while awaiting definitive emergency medical care.
 - Periodically visually inspect the naloxone solution through the viewing window. If the solution is discolored, cloudy, or contains solid particles, replace it with a new EVZIO.
 - Replace EVZIO before its expiration date.
-

Manufactured for:

kaleo, Inc.

Richmond, VA 23219

*For California Only: This product uses batteries containing Perchlorate Material – special handling may apply. See www.dtsc.ca.gov/hazardouswaste/perchlorate

PATIENT INFORMATION
EVZIO™ (EVV-zee-oh)
(naloxone hydrochloride injection)
Auto-Injector

You and your caregivers should read this Patient Information leaflet before an opioid emergency happens. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about EVZIO?

EVZIO is used to temporarily reverse the effects of opioid medicines. The medicine in EVZIO has no effect in people who are not taking opioid medicines. Always carry EVZIO with you in case of an opioid emergency.

1. Use EVZIO right away if you or your caregiver think signs or symptoms of an opioid emergency are present because an opioid emergency can cause severe injury or death. Signs and symptoms of an opioid emergency may include:
 - unusual sleepiness and you are not able to awaken the person with a loud voice or rubbing firmly on the middle of their chest (sternum)
 - breathing problems including slow or shallow breathing in someone difficult to awaken or they look like they are not breathing
 - the black circle in the center of the colored part of the eye (pupil) is very small, sometimes called “pinpoint pupils” in someone difficult to awaken
2. Family members, caregivers, or other people who may have to use EVZIO in an opioid emergency should know where EVZIO is stored and how to give EVZIO before an opioid emergency happens.
3. Get emergency medical help right away after using the first dose of EVZIO.
4. The signs and symptoms of an opioid emergency can return within several minutes after EVZIO is given. If this happens, give additional injections using a new EVZIO auto-injector every 2 to 3 minutes and continue to closely watch the person until emergency help is received.

What is EVZIO?

- EVZIO is a prescription medicine used for the treatment of an opioid emergency such as an overdose or a possible opioid overdose with signs of breathing problems and severe sleepiness or not being able to respond.
- EVZIO is to be given right away by a caregiver and does not take the place of emergency medical care. Get emergency medical help right away after the first dose of EVZIO, even if the person wakes up.

Who should not use EVZIO?

Do not use EVZIO if you are allergic to naloxone hydrochloride or any of the ingredients in EVZIO. See the end of this leaflet for a complete list of ingredients in EVZIO.

What should I tell my healthcare provider before using EVZIO?

Before using EVZIO, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems
- are pregnant or plan to become pregnant. Use of EVZIO may cause withdrawal symptoms in your unborn baby. Your unborn baby should be examined by a healthcare provider right away after you use EVZIO.

Tell your healthcare provider about the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use EVZIO?

Read the “Instructions for Use” at the end of this Patient Information leaflet for detailed information about the right way to use EVZIO.

- You should use EVZIO exactly as prescribed by your healthcare provider.
- Each EVZIO auto-injector contains only 1 dose of medicine.
- EVZIO should be injected into the muscle or skin of the outer thigh. It can be injected through clothing if needed.
- Caregivers should pinch the thigh muscle while injecting EVZIO into a child under the

age of one.

- A Trainer for EVZIO with a separate “Trainer Instructions for Use” leaflet is included with EVZIO. For additional training information and video instructions go to www.EVZIO.com or call 1-855-773-8946.
 - Practice with the Trainer for EVZIO before an opioid emergency happens to make sure you are able to safely use the real EVZIO in an emergency.
 - The Trainer for EVZIO does not contain a needle or medicine. It can be reused to practice your injection.
 - The red safety guard can be removed and replaced on the Trainer for EVZIO.

What are the possible side effects of EVZIO?

EVZIO may cause serious side effects, including:

• **Sudden opioid withdrawal symptoms.** In someone who has been using opioids regularly, opioid withdrawal symptoms can happen suddenly after receiving EVZIO and may include: body aches, fever, sweating, runny nose, sneezing, goose bumps, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, stomach cramping, increased blood pressure, and increased heart rate.

In infants under 4 weeks old who have been receiving opioids regularly, sudden opioid withdrawal may be life-threatening if not treated the right way. Signs and symptoms include: seizures, crying more than usual and increased reflexes.

These are not all of the possible side effects of EVZIO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EVZIO?

- Store EVZIO at room temperature between 59°F to 77°F (15°C to 25°C).
- Keep EVZIO in its outer case until ready to use.
- Occasionally check EVZIO through the viewing window of the auto-injector. The solution should be clear. If the EVZIO solution is discolored, cloudy, or contains solid particles, replace it with a new EVZIO.
- Your EVZIO has an expiration date. Replace it before the expiration date.

Keep EVZIO and all medicines out of the reach of children.

General information about the safe and effective use of EVZIO

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EVZIO for a condition for which it was not prescribed. You can ask your pharmacist or healthcare provider for information about EVZIO that is written for health professionals.

What are the ingredients in EVZIO?

Active ingredient: naloxone hydrochloride

Inactive ingredients: sodium chloride, hydrochloric acid to adjust pH, and water

EVZIO is not made with natural rubber latex.

Manufactured for kaleo, Inc., Richmond, VA, 23219

For more information, go to www.EVZIO.com or call 1-855-773-8946

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 4/2014

Instructions for Use EVZIO (EVV-zee-oh) (naloxone hydrochloride injection) Auto-Injector

Read the Instructions for Use that comes with EVZIO before using it. Talk to your healthcare provider if you or your caregivers have any questions about the use of EVZIO.

Automated voice instructions

EVZIO has a speaker that provides voice instructions to help guide you through each step of the injection. See Figure A. If the voice instructions do not work for any reason, EVZIO will still work. If this happens, use EVZIO as instructed below and follow the written instructions on the EVZIO auto-injector label.

Figure A



How to use EVZIO

Step 1. Pull EVZIO from the outer case. See Figure B.

Figure B

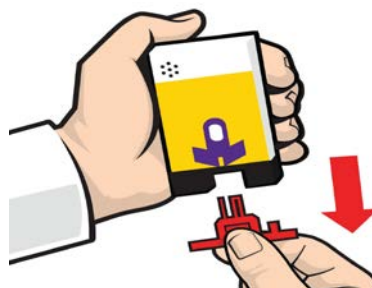


Do not go to Step 2 (Do not remove the **Red** safety guard.) until you are ready to use EVZIO. **If you are not ready to use EVZIO, put it back in the outer case for later use.**

Step 2. Pull off the **Red** safety guard. See Figure C.

To reduce the chance of an accidental injection, do not touch the **Black** base of the auto-injector, which is where the needle comes out.

Figure C



If an accidental injection happens, get medical help right away.

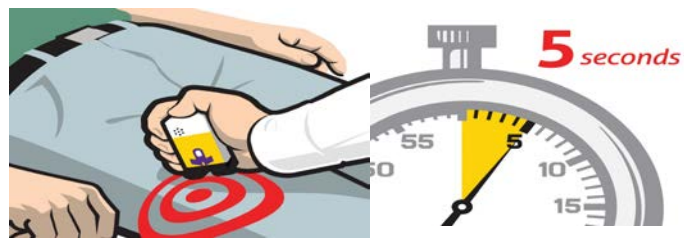
Note: The **Red** safety guard is made to fit tightly. **Pull firmly to remove.**

Do not replace the Red safety guard after it is removed.

Step 3. Place the **Black** end of EVZIO against the outer thigh, through clothing, if needed. **Press firmly** and hold in place for 5 seconds. See Figure D.

If you give EVZIO to an infant less than 1 year old, pinch the middle of the outer thigh before you give EVZIO and continue to pinch while you give EVZIO.

Figure D



Note: EVZIO makes a distinct sound (click and hiss) when it is pressed against the thigh. This is normal and means that EVZIO is working correctly. Keep EVZIO firmly pressed on the thigh for 5 seconds after you hear the click and hiss sound. The needle will inject and then retract back up into the EVZIO auto-injector and is not visible after use.

Step 4. After using EVZIO, get emergency medical help right away.

If symptoms return after an injection with EVZIO, an additional injection using another EVZIO may be needed. Give additional injections using a new EVZIO auto-injector every 2 to 3 minutes and continue to closely watch the person until emergency help is received.

EVZIO cannot be reused. After use, place the auto-injector back into its outer case. Do not replace the **Red** safety guard.

How to know that EVZIO has been used. See Figure E.

- The **Black** base will lock into place.
- The voice instruction system will state that EVZIO has been used and the LED will blink red.
- The **Red** safety guard cannot be replaced.
- The viewing window will no longer be clear. You will see a red indicator.

Figure E



What to do after EVZIO has been used:

- Get emergency medical help right away.
- Put the used EVZIO back into its outer case.
- Do not throw away the EVZIO in household trash. Do not recycle EVZIO.
- Used EVZIO should be taken to a healthcare setting for proper disposal in a sharps container.

There may be local or state laws about how to throw away used auto-injectors.*

*For California Only: This product uses batteries containing Perchlorate Material – special handling may apply. See www.dtsc.ca.gov/hazardouswaste/perchlorate

How should I store EVZIO?

- Store EVZIO at room temperature between 59°F to 77°F (15°C to 25°C).
- Keep EVZIO in its outer case until ready to use.
- Occasionally check EVZIO through the viewing window of the auto-injector. The solution should be clear. If the EVZIO solution is discolored, cloudy, or contains solid particles, replace it with a new EVZIO.
- Your EVZIO has an expiration date. Replace it before the expiration date.

Keep EVZIO and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for: kaleo, Inc., Richmond, VA 23219

Issued: 4/2014

Trainer for EVZIO™

Trainer Instructions for Use

Important:

The Trainer for EVZIO Does Not contain a needle or medicine. Always carry your real EVZIO with you in case of an opioid emergency.

Tell your family, friends, co-workers or other individuals who may need to use EVZIO during an opioid emergency, where you keep your EVZIO.

Important Information about the Trainer for EVZIO:

Inside your Trainer for EVZIO are:

- batteries
- a speaker that will make a beeping sound and that produces electronic voice instructions
- red and green blinking lights

The Trainer for EVZIO batteries are made to last for over 1,000 demonstrations or practices.

If the electronic voice instructions do not work properly, the Trainer for EVZIO can still be used for demonstration or practice. If this happens, use the instructions below and follow the written instructions on the Trainer for EVZIO label.

What is the Trainer for EVZIO?

- The Trainer for EVZIO does not contain a needle or medicine and can be reused to practice your injection.
- Practice with the Trainer for EVZIO before an opioid emergency happens to make sure you are able to safely use the real EVZIO in an emergency.
- A Trainer for EVZIO comes with each EVZIO prescription so that you and your caregiver can practice and demonstrate how to use EVZIO.

Figure A.



Trainer for EVZIO:

- is inside a **white and black** outer case
- **does not** contain a needle or medicine
- **can be** reused (the **Red** safety guard can be placed back on the **Black** base after use)
- **has no** expiration date

EVZIO:

- is inside a **purple and yellow** outer case
- contains a needle and medicine
- cannot be reused (the **Red** safety guard cannot be placed back on the **Black** base after it is removed)
- has an expiration date

In case of an opioid overdose or possible opioid overdose emergency, use the real EVZIO and not the TRAINER for EVZIO.

Who should practice using the Trainer for EVZIO?

Anyone who may need to help you with EVZIO in case of an opioid overdose or possible overdose emergency should practice using the Trainer for EVZIO.

Have them practice using the Trainer for EVZIO and review the Patient Information leaflet included in the packaging with your prescription of EVZIO.

For more information and video instructions on the use of EVZIO, go to <http://www.EVZIO.com> or call 1-855-77-EVZIO.

Practicing with the Trainer for EVZIO

- Practice with the Trainer for EVZIO before an opioid emergency happens to make sure you are able to safely use the real EVZIO in the case of an opioid overdose or possible overdose emergency.
- You and your caregivers should practice every day for the first week after you receive your Trainer for EVZIO, and then at least 1 time each week, to help you feel familiar with using EVZIO quickly and safely during an opioid overdose or possible opioid overdose emergency. Even when you are familiar with using the Trainer for EVZIO, continue to practice using it often.

How to use the Trainer for EVZIO

- Even though the Trainer for EVZIO does not have a needle and contains no medicine, it works the same way as the real EVZIO.
- Just like the real EVZIO, the Trainer for EVZIO contains an electronic voice instruction system to help guide you through each step of the injection. If the voice instructions do not work for any reason, you can still use the Trainer for EVZIO to practice using the instructions below and following the written instructions on the Trainer for EVZIO.
- The Trainer for EVZIO has the same blinking red and green lights as the real EVZIO. These blinking lights help provide visual cues for each voice instruction and step.

Follow these steps to practice using the Trainer for EVZIO

1. **Pull the Trainer for EVZIO from the outer case.** See Figure B.
2. **Pull off Red safety guard.** See Figure C.

Figure B



Figure C



Note: The **Red** safety guard is made to fit tight similar to the safety guard on EVZIO. **Pull firmly to remove.**

3. **Place Black end of the Trainer for EVZIO against the middle of the outer thigh (through clothing, if needed), then press firmly, and hold in place for 5 seconds.** See Figure D.

Figure D

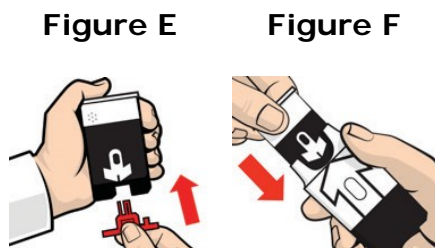


Only practice using the middle of the outer thigh. The outer thigh is where you would inject with the real EVZIO.

Note: The Trainer for EVZIO makes a distinct sound (click and hiss) when you press it against the outer thigh. This is the same sound that is made with the real EVZIO. This is normal, and indicates EVZIO is working correctly. Do not pull the Trainer for EVZIO away from the leg when you hear the click and hiss sound.

4. After practicing, reset the Trainer for EVZIO:

- a. Replace the Red safety guard.** See Figure E.
- b. Slide the Trainer for EVZIO all the way back into the white outer case to reset the electronic voice system.** See Figure F.



Note: Do not hold the Black base when replacing the Red safety guard. If you do this, the **Black** base may not reset properly and may prevent you from inserting the **Red** safety guard into the **Black** base. If this happens, remove the **Red** safety guard and repeat Step 4 above.

Leave the Trainer for EVZIO in its outer case for at least 5 seconds between each time you practice to allow the electronic voice system to reset.

How should I dispose of the Trainer for EVZIO?

The Trainer for EVZIO contains electronics and lithium coin cell batteries, and should be disposed of in the correct manner. Follow your State and local environmental regulations for disposal.

For California Only: This product uses batteries containing Perchlorate Material- special handling may apply. See www.dtsc.ca.gov/hazardouswaste/perchlorate

For more information or questions about the Trainer for EVZIO, go to www.EVZIO.com or call 1-855-773-8946.

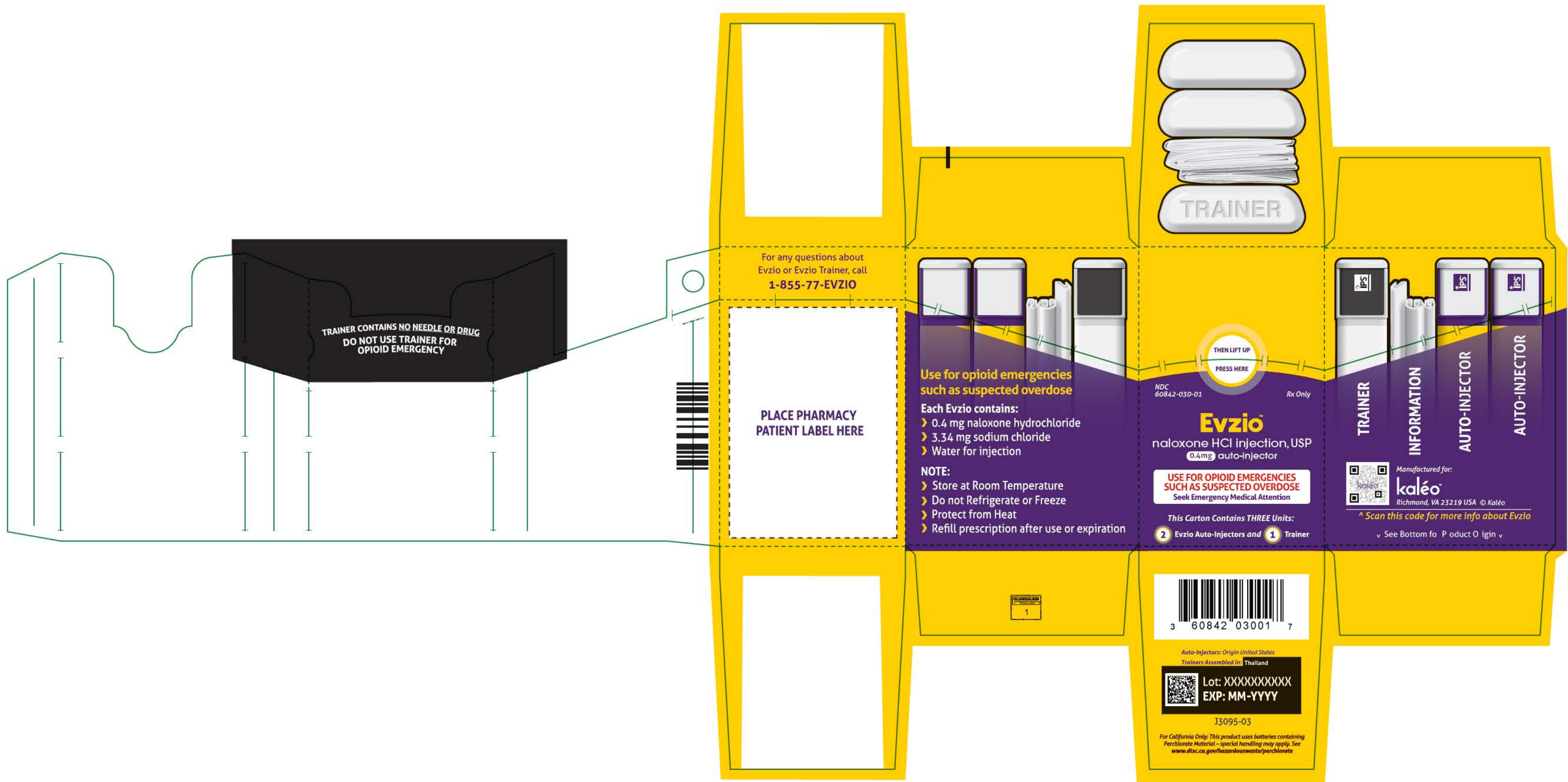
How should I store the Trainer for EVZIO?

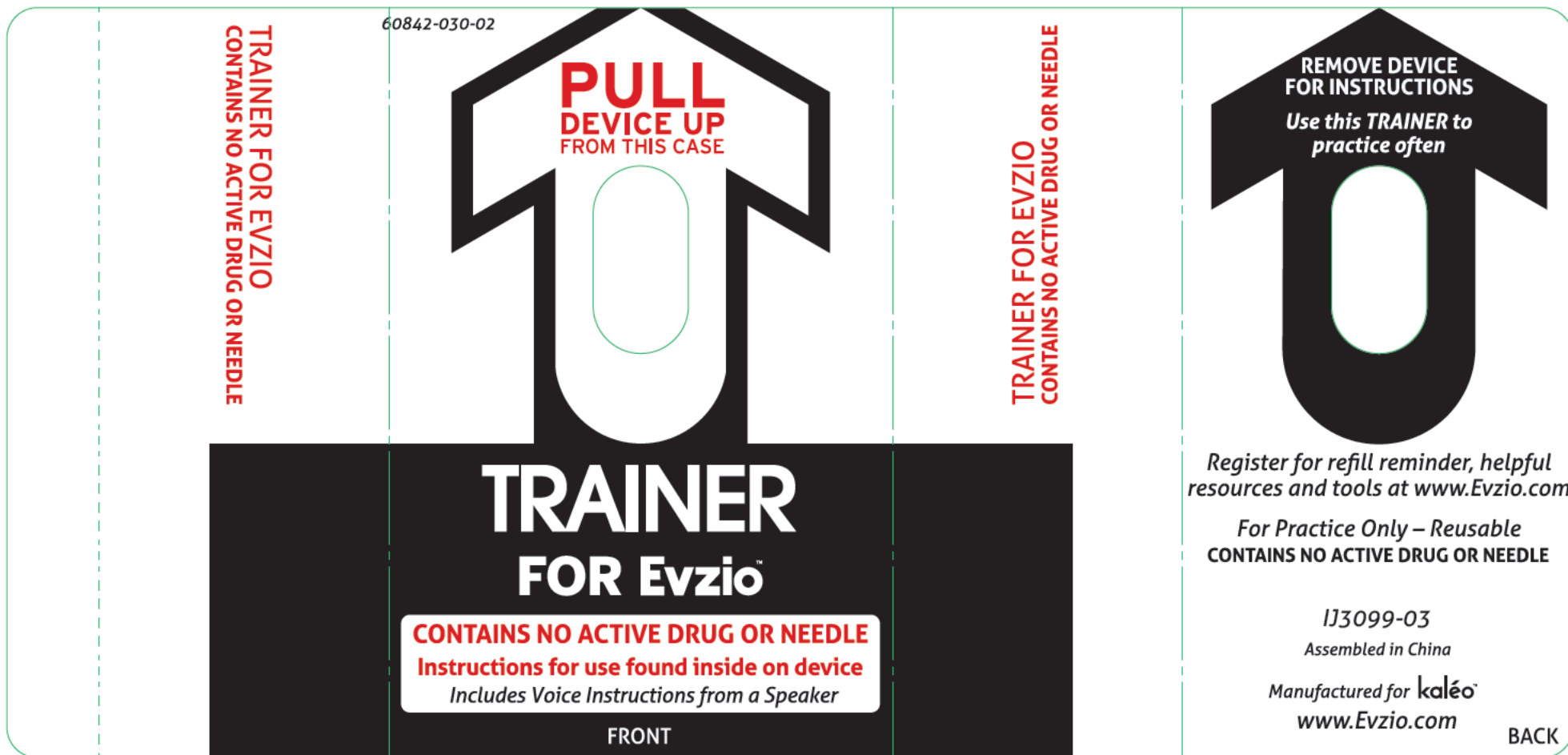
- Store the Trainer for EVZIO at room temperature between 59°F to 77°F (15°C to 25°C).
- Store the Trainer for EVZIO in its outer case.

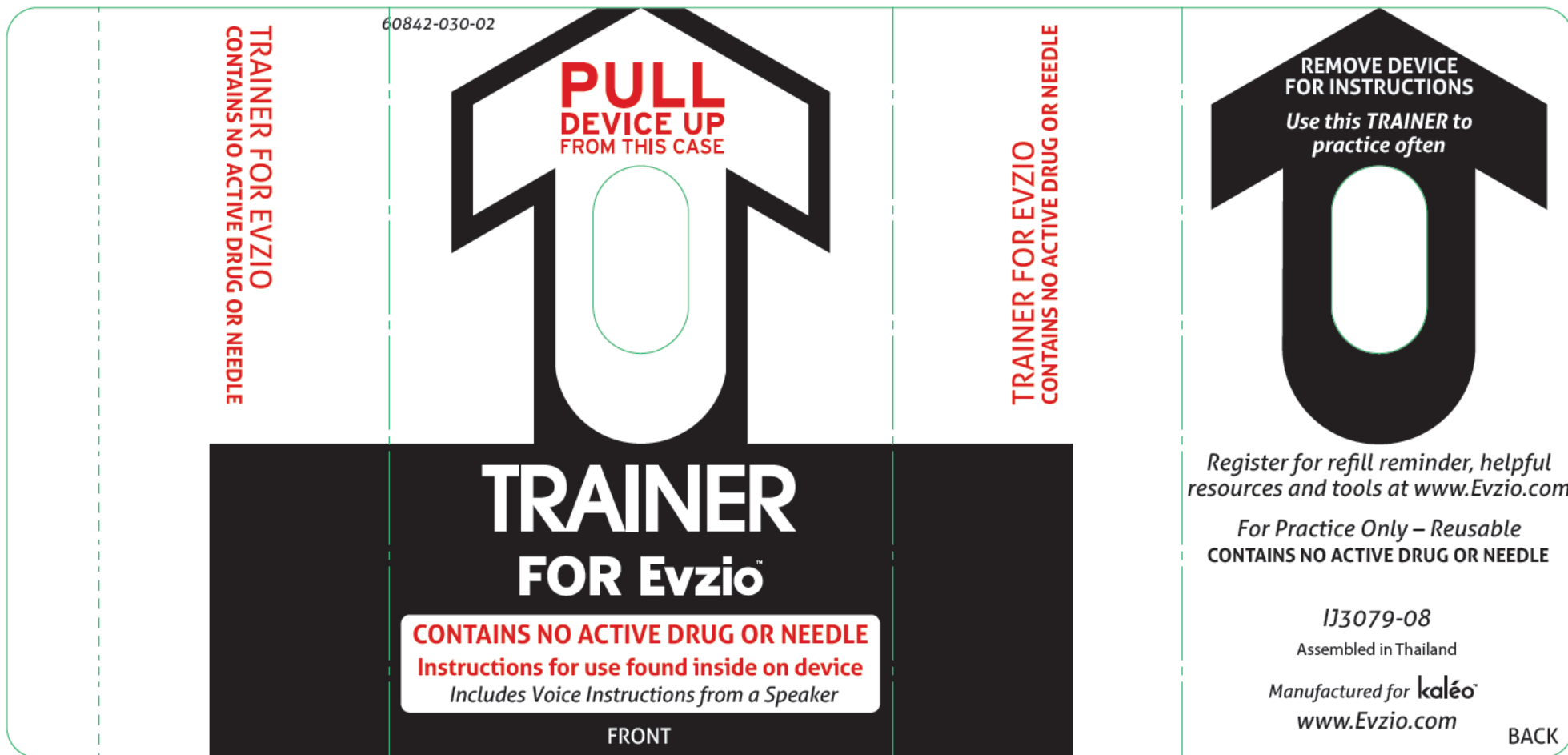
This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for kaleo, Inc. Richmond, VA 23219

Issued: 4/2014







TRAINER FOR EVZIO
CONTAINS NO ACTIVE DRUG OR NEEDLE



TRAINER FOR Evzio

CONTAINS NO ACTIVE DRUG OR NEEDLE



1
PULL OFF
RED Safety
Guard

FOR
PRACTICE
ONLY
REUSABLE



2
Place **BLACK**
END Against
Patient's
OUTER THIGH
Then **PRESS**
FIRMLY For
5 SECONDS.

CONTAINS NO ACTIVE
DRUG OR NEEDLE

KEEP FINGERS AWAY
FROM BLACK END

KEEP FINGERS AWAY
FROM BLACK END



Enabled with

Manufactured for **kaléo**

Richmond, VA 23219



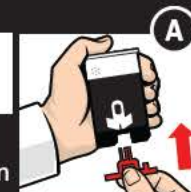
S/N: XXXXXXXX
MFG: XXXXX
LOT: XXXXX

IJ3078-06

TRAINER RESET INSTRUCTIONS

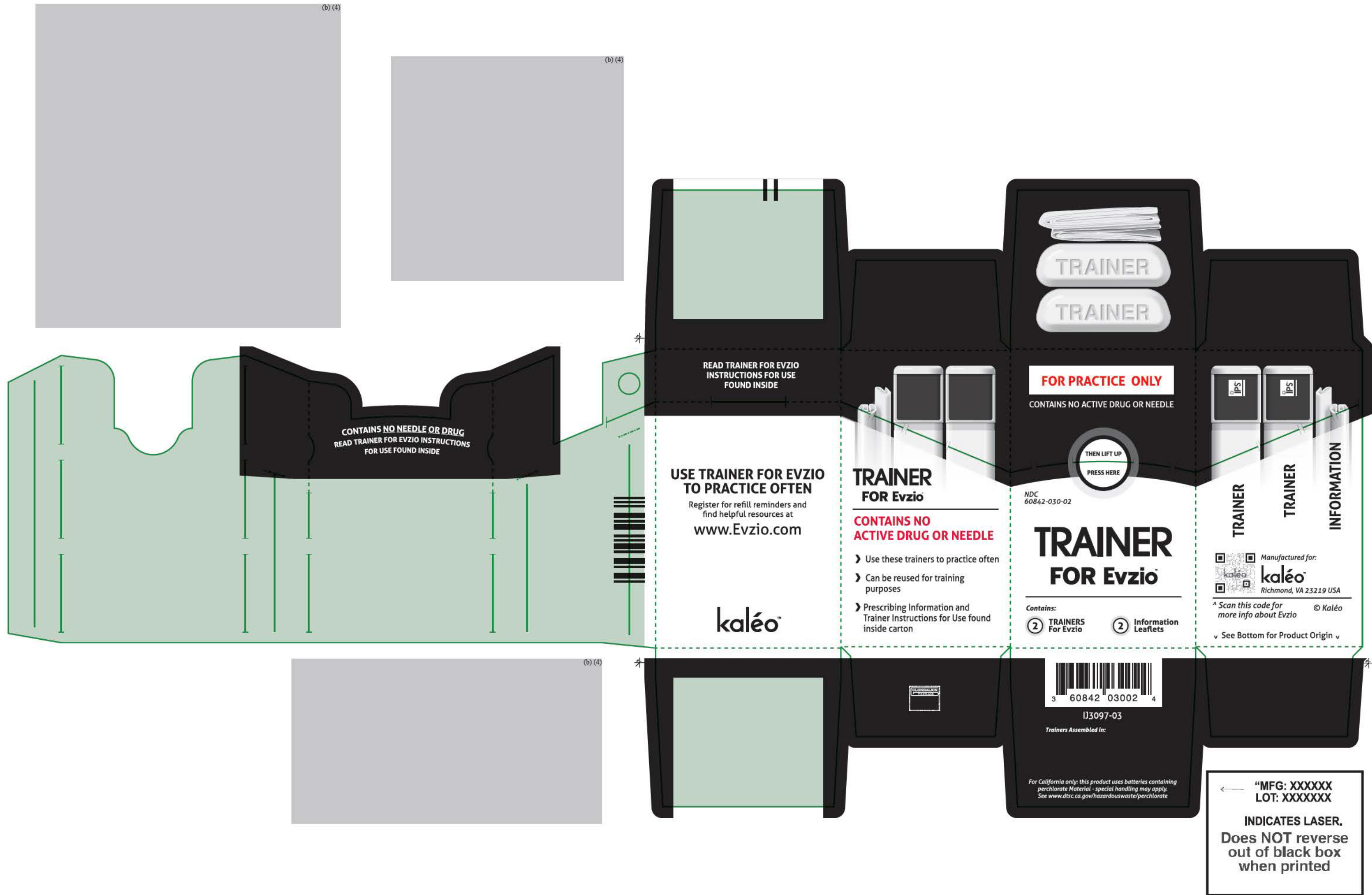
Replace **RED**
Safety Guard

Do Not Hold
Black Base When
Replacing Red
Safety Guard



Replace **WHITE**
Outer Case





REFILL PRESCRIPTION AFTER USE

NDC
60842 030 01

Rx Only

**PULL
DEVICE UP
FROM THIS CASE**

KEEP **Evzio** IN THIS CASE
UNTIL YOU NEED TO USE IT

FRONT

Evzio™

naloxone HCl injection, USP
0.4mg auto-injector

**USE FOR OPIOID EMERGENCIES
SUCH AS SUSPECTED OVERDOSE**

Seek Emergency Medical Attention

Instructions for use found inside on device
Includes Voice Instructions from a Speaker

TEXT "Exp" TO 3 13 151
TO RECEIVE EXPIRATION
DATE REMINDERS

**REMOVE DEVICE
FOR INSTRUCTIONS**
REPLACE IF
SOLUTION IS DISCOLORED, CLOUDY,
OR CONTAINS PARTICLES.

**DRUG VIEWING
WINDOW**

- Store at Room Temperature
- Do not Refrigerate or Freeze
- Protect from Heat



Manufactured for **kaléo**
www.Evzio.com

BACK

Page 86 of 236

Reference ID: 3482803 Code 39 barcode reads 1707.

- Each 0.4 mL contains:
- 0.4 mg naloxone hydrochloride
 - 3.34 mg sodium chloride
 - Water for injection

- After Use:
- Replace outer case
 - Ensure proper disposal
 - Refill prescription

Evzio
naloxone HCl injection, USP
autoinjector



PULL OFF
RED Safety
Guard

**FOR OPIOID
EMERGENCIES**



Place **BLACK**
END Against
Patient's
OUTER THIGH
Then **PRESS**
FIRMLY For
5 SECONDS.

Makes
CLICK AND
HISS SOUND
During
Injection

**SEEK EMERGENCY
MEDICAL ATTENTION**

**KEEP FINGERS AWAY
FROM BLACK END**

NEEDLE END

ips
Enabled with

Manufactured for **kaléo**
R chimand VA 23219

EXP: MM/YYYY
1 345678901
Lot: MA006



FOR SINGLE USE INJECTION

**SEE OTHER SIDE FOR
USE INSTRUCTIONS**

**DRUG VIEWING
WINDOW**

*Replace if solution is
discolored, cloudy, or
contains particles.*

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208411Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208411
Applicant Name	Adapt Pharma, Inc.
Date of Submission	July 20, 2015
PDUFA Goal Date	January 20, 2016
Proprietary Name / Established (USAN) Name	Narcan nasal spray / Naloxone hydrochloride
Dosage Forms / Strength	Intranasal spray / 40 mg/ml
Proposed Indication(s)	1. Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression 2. Intended for immediate administration as emergency therapy in settings where opioids may be present 3. Not a substitute for emergency medical care
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL Review	Joshua Lloyd, MD
Pharmacology Toxicology Review	Newton Woo, PhD, R. Daniel Mellon, PhD
OPQ Review	Venkat Pavuluri, PhD, Christina Capacci-Daniel, PhD, Erika Pfeiler, PhD, Grace McNally, PhD, Edwin Jao, PhD, Steve Kinsley, Julia Pinto, PhD
CDRH Review CDRH OCP	Ryan McGowan, Rick Chapman Juandria Williams
Clinical Pharmacology Review	Suresh Narahariseti, PhD, Yun Xu, PhD
OSI	Arindam Dasgupta, PhD, Yiyue Zhang, PhD, Melkamu Getie-Kehtie, PhD, RPh, Charles Bonapace, PharmD
OSE/DMEPA	Millie Shah, PharmD, BCPS; Vicky Borders-Hemphill, PharmD; Quynh Nhu Nguyen; MS, Irene Chan, PharmD, BCPS
OPDP/DCDP	L. Shene Toombs
OMP/DMPP	Nathan Caulk, MS, BSN, RN; Barbara Fuller, RN, MSN, CWOCN; LaShawn Griffiths, MSHS-PH, BSN, RN
Pediatric Maternal Health Staff	Mona Khurana, MD; Hari Cheryl Sachs, MD; Linda Lewis, MD

OND=Office of New Drugs

OPQ= Office of Pharmaceutical Quality

OCP = Office of Combination Products

DMEPA=Division of Medication Errors Prevention

OPDP=Office of Prescription Drug Promotion, DCDP=Division of Consumer Drug Promotion

OMP=Office of Medical Policy Initiatives, DMPP=Division of Medical Policy Programs

CDTL=Cross-Discipline Team Leader

CDRH=Center for Device and Radiological Health

OSE= Office of Surveillance and Epidemiology

OSI=Office of Scientific Investigations

Signatory Authority Review Template

1. Introduction

The current application is a 505(b)(2) application for Narcan (naloxone hydrochloride) Nasal Spray which cross references the efficacy and safety information from Narcan, (NDA 016636). This application represents the first nasal naloxone spray to meet the criteria for novel naloxone products described by the Agency during the public meetings held in 2012 and in 2015. The application was accepted for rolling review and was granted priority review status upon submission of the final sections reflecting the importance this product from the public health perspective. The application relies on a relative bioavailability study in healthy volunteers. As the marketing of Narcan has been discontinued, the Applicant used a generic product, International Medicinal System's naloxone HCl injection USP pre-filled syringe (ANDA 072076) for the relative bioavailability study necessary to create a scientific bridge to the Agency's prior findings for Narcan. This review will focus on the pharmacokinetic parameters, local adverse events, and the potential for use in pediatric overdose situations.

2. Background

Naloxone HCl was first approved in 1971(Narcan, NDA 016636), for intravenous, intramuscular, and subcutaneous administration. The current labeling of Narcan recommends an initial dose of 0.4 mg to 2 mg, followed by repeated doses up to 10 mg in the setting of suspected opioid overdose. The off-label use of commercially available naloxone hydrochloride by the intranasal route of administration using a nasal atomizer is growing in popularity as many programs and communities seek to address the public health problem of prescription and illicit opioid abuse and the overdoses that occur in these settings. The need for a naloxone product for use outside of a controlled medical setting extends beyond the setting of abuse. As the management of chronic pain in the US relies heavily on the use of chronic opioid treatment, there is risk for overdose for patients and household contacts. The first product approved to address the risk of opioid overdose in all settings was Evzio (naloxone HCl injection), approved on April 3, 2014. Evzio is an autoinjector with audible and written instructions for use, and delivers 0.4 mg of naloxone in 0.4 mL to the subcutaneous or intramuscular space.

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, there are no data that specifically quantitate the success rate, leaving the question of whether there are situations that could have benefited from a higher dose of naloxone. Unpublished pharmacokinetic data suggest that naloxone levels following off-label use by the intranasal route are lower than by the approved routes of administration. The lowest effective dose of naloxone is unclear, and is likely dependent on a number of factors, including dose, route of administration, and the amount and

type of opioid involved in the overdose. In discussion with the Applicant during product development, it was determined that designing an efficacy study to define an effective range of naloxone use in the proposed setting would be difficult to justify as it would require administration of opioids to create an overdose, albeit in a controlled setting. The use of pharmacodynamic measurements such as pupil dilation or response to inhaled carbon dioxide may demonstrate an effect of naloxone, however, because the relationship between experimental opioid effects and reversal of a clinically meaningful overdose is not well defined, could not be relied upon for dose selection. Furthermore, there is an approved dosing regimen for naloxone. Therefore, the approach required by the division was to match the naloxone exposure achieved by administration of naloxone using an approved dose and route. This is done by conducting a relative bioavailability study that demonstrates the new product matches or exceeds the pharmacokinetic parameters of Cmax and Tmax for naloxone by an approved route, intramuscular, intravenous, or subcutaneous injection. The first few minutes are of particular importance, because if the overdose has led to apnea, time is of the essence if the brain is to be spared permanent hypoxic injury. Therefore, in addition to Cmax and Tmax, it is necessary to demonstrate that the naloxone levels are comparable to the approved route during the first minutes after dosing. Given the known safety profile of naloxone, the relative bioavailability study can be conducted in a normal healthy volunteer population without risk to the study participants. This approach has been discussed at two public meetings hosted by FDA.^{1,2}

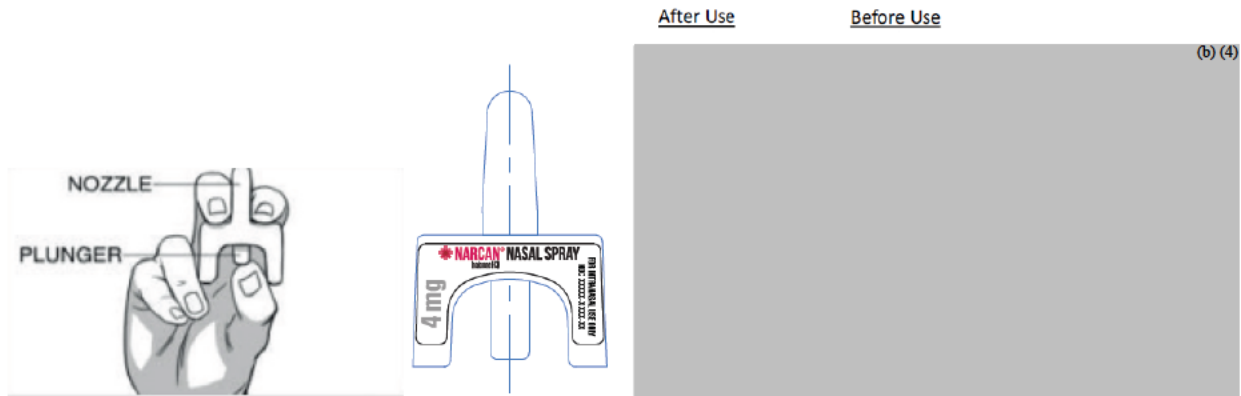
In patients managed with opioid analgesics, an opioid overdose leading to death can occur in a variety of settings. Patients may inadvertently take too much trying to better manage pain, or through errors in dose or frequency. Initiating a new concomitant medication that inhibits the metabolic pathway of an opioid, or discontinuation of a concomitant medication that induces the metabolic pathway can result in overdose in a patient who has used their opioid analgesic according to instructions. Addition of a new medication with the adverse effect of central nervous system depression, or an error in judgment surrounding the use of alcohol can also create a situation of over sedation in a patient previously stable on an opioid. Overdose can occur in household contacts of a patient prescribed opioids by accidental exposure or through intentional misuse or abuse. Individuals abusing prescription opioid analgesics or illicit opioids can also inadvertently overdose. With the range of potency of available opioids, death from overdose can occur with the first attempt at abuse. Death due to overdose from most opioids may be preventable with the immediate administration of an opioid antagonist such as naloxone. However, there are limitations in the prevention of death in this setting. The effects of some opioids such as buprenorphine may be difficult to antagonize. Larger doses of antagonist may be necessary than are available and the opioid overdose must be reversed before hypoxia results in irreversible injury. Also, it is important to realize that the duration of antagonists such as naloxone are generally shorter than the duration of action of most opioids. Therefore, even when an antagonist is available, it is no substitute for seeking emergency medical help.

¹Exploring Naloxone Uptake and Use – A Public Meeting, July 1 and 2, 2015.
<http://www.fda.gov/Drugs/NewsEvents/ucm442236.htm>

² Role of Naloxone in Opioid Overdose Fatality Prevention; Request for Comments; Public Workshop, April 12, 2012. <http://www.fda.gov/Drugs/NewsEvents/ucm277119.htm>

3. OPQ/Device

Narcan Nasal Spray consists of the formulated drug product filled into a unit-dose vial which is stoppered and placed within a Unit-dose Delivery Device produced by (b) (4). This unit-dose device is then placed into a single blister pack. The container closure-spray device is a single-entity combination (drug/device) product. The device contains 100 microliters of a 40 mg/mL solution of naloxone hydrochloride, and is intended to deliver a dose of 4 mg with one spray. The device is displayed in the following figures:



From the Office of Pharmaceutical Quality review:

The naloxone API is supplied by (b) (4). The drug product is formulated in (b) (4) comprising the following excipients: Sodium chloride, (b) (4) and benzalkonium chloride, in a concentration of 40mg/ml. The container closure system is a glass vial with a (b) (4) stopper which is then encased within a nasal actuator and container holder. The nasal spray device is by (b) (4), under DMF (b) (4), and has been reviewed by CDRH and OPQ, for use with the naloxone drug product. Each unit dose device, formulated to deliver one dose of naloxone, is placed within a blister package. Two units or blister packages are then stored per carton. Adequate data to assess the device delivery of the drug product and to assure the identity, strength, purity, and quality of the drug product is provided. The drug product is granted an expiry of 24 months, when stored at room temperature. Further, the Office of Process and Facilities, has made an overall recommendation of adequate for all facilities related to this application. Therefore, from a quality perspective, this NDA is recommended for approval.

Mr. McGowan performed an evaluation of the design of the device constituent parts of the combination product and covered the intended design and design control information for the subject device constituent part. From Mr. McGowan's review:

The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the of the device constituent parts of the subject combination product. After examination of the original new drug application (NDA), cross-referenced drug master files (DMF), and responses to information requests, the consulting reviewer has determined that the device constituent parts of the

combination product have been designed appropriately for the product's intended use and essential performance requirements have been verified with a reasonable degree of certainty at a time period shortly after manufacture.

The reviewer was not able to locate information which assures that the combination product is free from unacceptable risk with respect to the potential for under-dose or failure-to-dose events. Specifically, the sponsor has not demonstrated that a population of manufactured product is able to activate reliability after conditioning to applicable environmental or physical effects.

The consulting reviewer discussed the lack of reliability information available within the submission record with CDER/OND/ODEII/DAAAP within a September 23, 2015 mid-cycle meeting and an October 22, 2015 wrap-up meeting. The review division agreed with the consulting reviewer's assessment that additional information is needed regarding combination product reliability, however given the benefits of the product; the review division determined that this information could be requested within a post-market commitment or post-market requirement. Please see the final section of this review memorandum for recommended post-market commitment/requirement language regarding combination product reliability.

Therefore, the consulting review finds this submission to be approvable for device constituent part design considerations and requests commitment from the sponsor to engage in post-market activities to verify combination product reliability.

As discussed by Dr. Lloyd in his review:

Mr. McGowan determined that "the device constituent parts of the combination product have been designed appropriately for the product's intended use and essential performance requirements have been verified with a reasonable degree of certainty at a time period shortly after manufacture." However, Mr. McGowan notes that the application contains inadequate information to demonstrate that the manufactured product is able to activate reliably after exposure to a variety of real-world conditions. There is a potential for under-dose or failure-to-dose events leading to undertreated, life-threatening CNS and respiratory depression as a consequence of a device failure under these conditions.

Also noted by Dr. Lloyd in his review:

Mr. McGowan found the device-related product specifications acceptable with the exception of dose content uniformity, which allowed for relatively wide batch release specifications. This specification requires that (b) (4)

Given the relatively wide safety margin with naloxone, there is little concern for the upper limits of these release specifications, particularly since Narcan is labeled with dosing recommendations up to a total of 10 mg of naloxone. In general, the greatest concern would be for releasing a batch that might not deliver an adequate dose of naloxone in an immediately life-threatening situation. However, given the pharmacokinetic profile of this product (refer to Section 5 below), which achieves much higher systemic exposures to naloxone than the approved comparator dose of naloxone (i.e., 0.4 mg IM), the lower

limit of these specifications are also acceptable. Additionally, Narcan nasal spray should only be made available in a two-pack configuration, (b) (4) (refer to Section 12 below for additional discussion), ensuring that a second dose is available in the event of an inadequate response.

The postmarket requirement recommended by Mr. McGowan is as follows:

1. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability as described in detail below:
 - Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as $R(t) = x\%$, where t = time and $x\%$ = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after preconditioning to elements outlined within c, below. The reliability requirements should be verified with a high degree of statistical confidence.
 - Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.
 - Perform a test to verify the reliability requirements specified in above.
 - Devices assessed within the reliability test should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete.
 - Shipping
 - Aging
 - Storage orientation and conditions
 - Vibration handling
 - Shock handling (e.g., resistance to random impacts, such as being dropped)
 - Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however you should provide rationale supporting the final circumstances of activation chosen.
 - Activation orientation
 - Environmental temperature
2. Establish a post-market monitoring program for detection and evaluation of under-dose and failure-to-dose events, regardless of cause, and provide periodic reports to the Agency which contain descriptions of each reported event along with results of root-cause and contributing-cause analyses.

I concur with the conclusions reached by the OPQ review team and the CDRH reviewer regarding the acceptability of the manufacturing of the drug product, drug substance, and

device. While Mr. McGowan has found that the reliability has not been formally documented, leading to the PMR, there is considerable experience with the nasal spray device by (b) (4) leading to a low suspicion that there will be a problem with reliability. Further, Mr. McGowan noted wide batch release specifications for the dose content uniformity. As will be discussed in the Clinical Pharmacology Section, the amount of naloxone and resultant exposure in each dose of the Narcan Nasal Spray are large enough to assure that even at the low end of the specifications, a large enough dose of naloxone will be delivered to expect efficacy. Further, as noted by Dr. Lloyd, the product will be available only in two-pack configurations so that a second dose will be available if needed.

Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues that preclude approval. I concur with the recommended PMR.

4. Nonclinical Pharmacology/Toxicology

From Dr. Woo's review:

The Applicant did not submit any new nonclinical studies to support this marketing NDA as none were required. Local tolerance studies would normally be required to support a reformulated drug product that employs an alternate route, however, the Division determined that nonclinical studies would not be required given the clinical experience with intranasal naloxone, lack of any novel excipients, the acute use of the drug product, and the potentially life-saving indication.

The Applicant has provided adequate data to support the safety of the drug substance, drug product, and drug product formulation. To support the safety of the container closure system, the Applicant has submitted extractables data under various extraction conditions. Under the most relevant solvent condition using water, no peaks were present indicating that there were no compounds that appeared after harsh extraction conditions. It is notable that a leachables assessment was not conducted but the Applicant has indicated that potential leachables will be evaluated in long-term stability samples. It is in the opinion of this Reviewer that the absence of leachables data does not preclude marketing approval for the following reasons: 1) the (b) (4) plungers is used in other FDA-approved aqueous based nasal and injectable drug products; 2) analysis of water extracts did not identify any substances; 3) the Applicant has committed to monitor for leachables during stability; 4) most importantly, this product is indicated for an acute, single-use indication; and 5) the drug product is a potentially life-saving therapy. The Applicant has committed to monitoring batches on stability for leachables. This should be solidified as a formal post-marketing commitment (PMC).

The PMC recommended by Dr. Woo is:

As proposed, conduct and submit an adequate leachable safety assessment for your drug product and container closure system. This assessment must include leachable data from long-term stability studies taking into consideration the proposed shelf-life to determine if the specified extractables also leach into the drug product over time, and a toxicological risk assessment justifying the safety of the leachables taking into consideration the maximum daily dose of the identified materials for this drug product.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval and with the PMC described.

5. Clinical Pharmacology/Biopharmaceutics

The basis for efficacy for Narcan Nasal Spray cross reference to the efficacy and safety information from Narcan and the relative pharmacokinetic profile of naloxone from this new Nasal Spray. The key study as described by Dr. Lloyd:

The Applicant conducted study Naloxone-Ph1a-002 (also referred to as study 002, in this review), a pivotal relative bioavailability study, in support of this application to establish a scientific bridge to their NDA for Narcan (NDA 16636) in order to establish the safety and efficacy of Narcan nasal spray.

Study 002 was an open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover study conducted in 30 adult male and female healthy volunteers in an inpatient setting to evaluate the pharmacokinetics of two doses of Narcan nasal spray (i.e., 4 mg [one spray in one nostril] and 8 mg [one spray in each nostril]) in comparison to an approved generic version of naloxone given intramuscularly (i.e., 0.4 mg). Two doses of another formulation of intranasal naloxone that are not the to-be-marketed formulation were also evaluated in this study. Subjects were assigned to one of five sequences, with six subjects planned in each sequence. A four-day washout period separated the treatments. Narcan nasal spray was administered using an (b) (4) single-dose device (b) (4) with the subject in a fully supine position. The left nostril was used for the 4-mg dose, and one spray was administered into each nostril for the 8-mg dose. Subjects were instructed not to breathe through the nose during administration of Narcan nasal spray and remained fully supine for approximately one hour post-dose. Intramuscular (IM) naloxone was administered as a 1-ml (i.e., 0.4 mg/ml) single injection into the gluteus maximus muscle using a 23-gauge needle.

The following figure and two tables from Dr. Naraharisetti's review demonstrate the naloxone levels for one spray of Narcan Nasal Spray into one nostril, two sprays of Narcan Nasal Spray as one spray into each nostril, and an intramuscular injection of 0.4 mg of naloxone. The critical findings supporting the expected efficacy of Narcan Nasal Spray are best captured by the exposure in the first five minutes following dosing. The naloxone levels from one nasal spray rise as early as from the intramuscular injection and peak higher.

Figure Mean plasma concentration time profiles of naloxone from 0 to 4 hours following

intranasal and intramuscular naloxone administration to healthy subjects (N = 29)

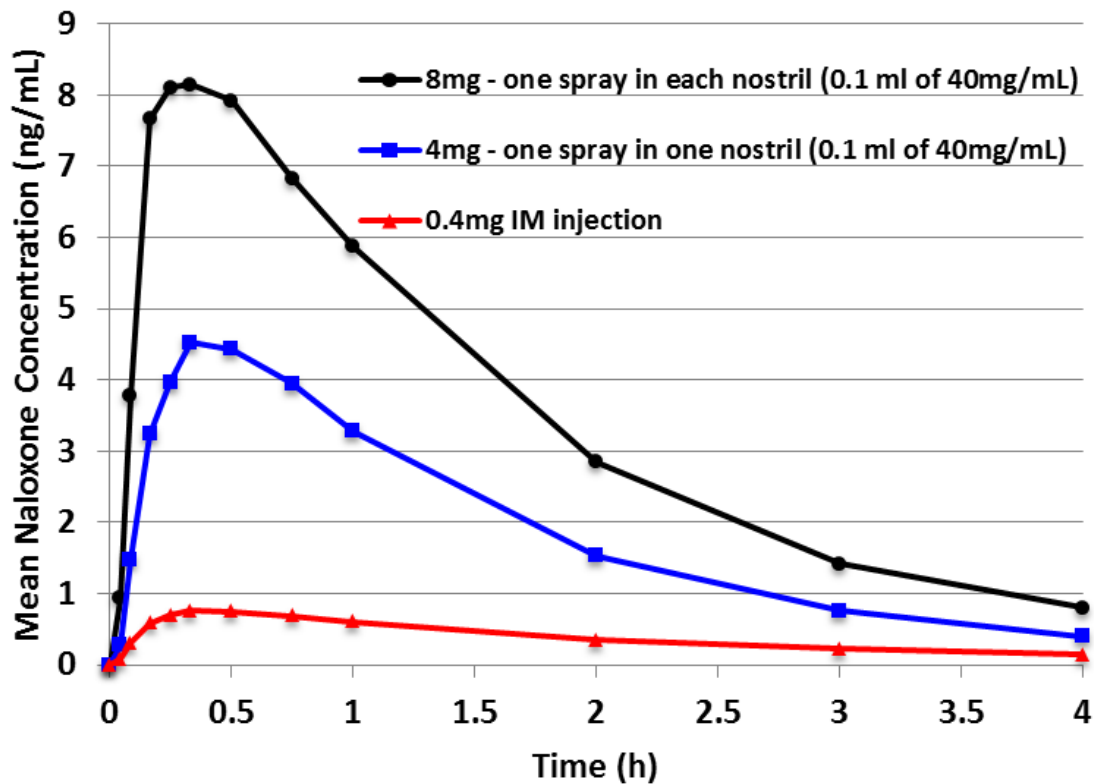


Table Geometric mean ratios and 90% CIs for plasma naloxone pharmacokinetic parameters following intranasal and intramuscular administration.

Parameter	Test Vs Reference	Adjusted Geometric LS mean		Ratio % [Test/Reference] (lower, upper 90% CI of ratio)
		Test (n=29)	Reference (n=29)	
C _{max} (ng/mL)	4 mg -one IN Spray in one nostril (Test) Vs 0.4 mg IM (Reference)	4.83	0.870	555 (464, 665)
AUC _{0-t} (h*ng/mL)		7.90	1.68	469 (418, 527)
AUC _{0-inf} (h*ng/mL)		7.99	1.73	462 (412, 519)
C _{max} (ng/mL)	8 mg -one IN Spray in each nostril (Test) Vs 0.4 mg IM (Reference)	9.62	0.870	1110 (925, 1320)
AUC _{0-t} (h*ng/mL)		15.0	1.68	890 (793, 999)
AUC _{0-inf} (h*ng/mL)		15.2	1.73	878 (783, 985)

Table Comparison of mean naloxone concentrations between IM injection and NARCAN one spray in one nostril or one spray in each nostril from 2.5 to 60 minutes post dose.

Time post-dose after naloxone drug product administration (minutes)	Mean Concentration (ng/mL) (% CV) N=29			Fold higher naloxone concentration:	Fold higher naloxone concentration:
	Reference	Test	Test		
	IM injection (0.4 mg)	One IN spray in one nostril (4mg)	One IN spray in each nostril (8mg)	One IN spray (4mg) Vs. IM injection (0.4 mg)	One IN spray in each nostril (8mg) Vs. IM injection (0.4mg)
2.5	0.079 (168)	0.28 (151)	0.93(131)	3.5	11.8
5	0.306 (108)	1.48 (117)	3.78 (105)	4.8	12.3
10	0.578 (55)	3.24 (67)	7.66 (68)	5.6	13.3
15	0.696 (46)	3.97 (56)	8.10 (44)	5.7	11.6
20	0.754 (36)	4.53 (50)	8.14 (31)	6.0	10.8
30	0.749 (25)	4.43 (43)	7.92 (25)	5.9	10.6
45	0.684 (25)	3.95 (41)	6.83 (24)	5.8	10.0
60	0.604 (24)	3.28 (37)	5.87 (23)	5.4	9.7

This pharmacokinetic profile from Narcan Nasal Spray demonstrates that a nasal spray can be formulated to result in efficacy comparable to the use of naloxone by intramuscular injection. In this case, the 4 mg dose of Narcan Nasal Spray provides naloxone concentrations ranging from 3.5-fold to 6-fold higher than a 0.4 mg intramuscular injection.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not Applicable.

7. Clinical/Statistical-Efficacy

No new clinical efficacy studies were submitted in support of this application. The Applicant is relying on cross reference to the efficacy and safety information from Narcan (naloxone hydrochloride), NDA 016636.

8. Safety

There were no new safety studies submitted in support of this application. Two relative bioavailability studies were conducted in normal volunteers, but as only Study 002 used the final to-be-marketed formulation, the safety data from this study will be used for product labeling along with information from the referenced drug.

As described by Dr. Lloyd:

In study 002, there were a total of 87 single exposures of Narcan nasal spray to a nostril (Table 3). Thirty unique subjects received Narcan nasal spray, including 28 subjects who received both 4 mg in one nostril and 4 mg in each nostril (8 mg total dose), 1 subject who received 4 mg in one nostril only (subject was discontinued due to an adverse event), and 1 subject who received 4 mg in each nostril (8 mg total dose) but not 4 mg in one nostril (discontinued at the subject's request), as summarized in Table 4. The extent of exposure and nasal irritation monitoring are adequate to evaluate the potential for local toxicity.

There were no deaths or serious adverse events during the clinical pharmacology studies. One subject was discontinued for because of elevated blood pressure measurements on the day prior to dosing of the second treatment period.

From Dr. Lloyd's review:

There were 27 adverse events (AEs) reported by 17 subjects. All AEs were considered mild in severity except for the one subject who experienced a moderate increase in blood pressure that lead to discontinuation. Table 6**Error! Reference source not found.** lists all AEs that occurred in study 002. The list of AEs for a particular treatment includes all AEs recorded beginning with the administration of that treatment until the next treatment administration in the sequence. The Narcan nasal spray groups (40 mg/ml formulation) are highlighted in yellow in the table. AEs reported for subjects in the Narcan nasal spray groups included increased blood pressure, musculoskeletal pain, headache, and xeroderma, in addition to AEs indicative of local nasal irritation, including nasal dryness, nasal edema, nasal congestion, and nasal inflammation. The IM naloxone comparator arm reported nausea, dizziness, and headache.

These safety findings are acceptably balanced by the potential benefit of Narcan Nasal Spray.

Naloxone is generally not administered outside of the setting of a suspected opioid overdose. Based on the adverse events reported in the labeling for Narcan, in the setting of an opioid-tolerant patient, administration of naloxone can result in precipitation of an acute withdrawal syndrome characterized by body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, and tachycardia. In the neonate, opioid withdrawal signs and symptoms also included: convulsions, excessive crying, and hyperactive reflexes.

Also as noted in the labelling for Narcan, in the postoperative setting, there have been post-marketing reports of hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation.

There is minimal to no risk from administration of a dose of 4 mg of intranasal naloxone to a person who has not had an opioid overdose if the person is not opioid-tolerant. In the setting of a patient who is obtunded with respiratory depression, if the cause is not opioid overdose, no ill effect is expected, the instructions to seek emergency medical care are appropriate, and use of Narcan nasal spray should not result in substantial delay in seeking that emergency care.

9. Advisory Committee Meeting

This application was not taken to an advisory committee meeting. There were no issues that arose during the review period requiring external advice.

10. Pediatrics

Pediatric patients and children may be at risk for an opioid overdose in the community as a result of several scenarios. Similar to adults, pediatric patients may receive an inadvertent overdose based on an error in dosing (too soon, too much), initiation of a concomitant drug that inhibits metabolism of the opioid, or cessation of a concomitant drug that had induced the metabolism of the opioid. In addition, children in a home where opioids are in use may come in contact with an opioid through improper storage or disposal with the risk of resultant overdose. Older children may experiment with opioid analgesics in an attempt to get high and inadvertently overdose. Therefore, pediatricians caring for pediatric patients prescribed opioids or caring for children who are otherwise well, but may be at risk for coming in contact with an opioid, may find it appropriate to prescribe naloxone to be kept in the home as a safety precaution.

The package insert for Narcan includes pediatric labeling as follows:

USAGE IN CHILDREN

- Narcotic Overdose—Known or Suspected: The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone may be administered I.M. or S.C. in divided doses. If necessary, naloxone hydrochloride injection can be diluted with sterile water for injection.

This is in contrast to the following dosing regimen in adults:

USAGE IN ADULTS

- Narcotic Overdose—Known or Suspected: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of narcotic-induced or partial

narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

The efficacy of Narcan Nasal Spray in pediatric patients is based on cross reference to the efficacy findings for naloxone as described in the labeling for Narcan for injection. Narcan Nasal Spray can be expected to be effective, settings where a child has signs of an opioid overdose requiring emergency treatment.

There is, however, a narrow set of situations in which a naloxone product that can be titrated to effect and/or is administered by a route other than the nasal route may be better suited. Neonates born to mothers using prescription opioids to manage pain or to treat opioid dependence or using illicit opioids may require an opioid antagonist to reverse respiratory depression immediately after birth. Rather than risking an abrupt precipitation of withdrawal symptoms with a large dose of naloxone, it would better serve the infant to use naloxone for injection dosed according to standard protocols and titrated to effect. Furthermore, infants under two months of age are obligate nose breathers and there is a small risk that use of a nasal spray in these infants could result in apnea. Some of these infants may be managed with a slow opioid taper once they are discharged to go home. In this setting, it is important to consider having a naloxone product available in case a problem with opioid overdose arises, and other products, such as the approved naloxone autoinjector may be more appropriate than a nasal spray.

As the first nasal spray formulation of naloxone, Narcan Nasal Spray triggers the requirements for pediatric studies under the Pediatric Research Equity Act. This raises a number of regulatory challenges. In contrast to adults, pharmacokinetic studies cannot be conducted in healthy children, while as with adults, efficacy studies are not possible either.

The following is from Dr. Lloyd's review:

Therefore, the Applicant was required to support the safety and efficacy of Narcan nasal spray in pediatrics, based on a review of available information, including the published literature, clinical practice guidelines, and the approved labeling for Narcan. This 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
- Justification for the proposed dosing volume in all pediatric patients, including neonates
- Justification for why the absorption of drugs through the nasal mucosa will not be different in pediatric patients, including neonates, compared to adults
- A device (e.g., nasal tip) that can appropriately deliver the correct volume to all pediatric patients, including neonates

The Applicant received an agreed upon pediatric study plan (PSP) on June 22, 2015, which included a plan to submit the required pediatric assessment with the NDA. The Division of Pediatric and Maternal Health (DPMH) was consulted to evaluate the

adequacy of the pediatric assessment to support approval in the full pediatric age range and the proposed labeling.

Dr. Lloyd goes on to summarize the consultative input from the Division of Maternal and Pediatric Health and the discussion at the Pediatric Research Committee:

DPMH recommended “approval for the proposed indication for pediatric patients from birth to under age 17 years for emergency treatment of known or suspected opioid overdose until emergency medical services can be provided by trained professionals,” provided that “DAAAP is satisfied that IN delivery with the proposed unit dose device will result in absorption of a minimally effective dose in pediatric patients of all ages.”

DPMH raised concerns in their review about the safety of the proposed product as it relates to IN drug delivery. Specifically, DPMH requested DAAAP to confirm that the actuator tip may be properly positioned and, based on concerns of differences in nasal morphology, can deliver a minimally effective dose in pediatric patients under five years of age. Further, given the fixed dose, DPMH raised concerns that the 4-mg dose could deliver a dose approximately 100-fold higher than what is recommended in Narcan labeling if the full dose is systemically absorbed. DPMH raised additional concerns for the potential to induce respiratory distress with intranasal instrumentation in the youngest patients because of obligate nasal breathing.

Therefore, DPMH recommended a postmarketing requirement (PMR) and a postmarketing commitment (PMC) to, respectively, capture any treatment failures or serious AEs of airway obstruction, respiratory distress, or respiratory arrest in pediatric patients under one year of age and evaluate the pharmacokinetic profile of this product in patients under five years of age.

This application was discussed at a meeting of the Pediatric Review Committee (PeRC) on November 4, 2015, where the above PMC and PMR were initially discussed.

This will be conveyed in the package insert in Sections 5.3 and 8.4 as follows:

5.3 Precipitation of Severe Opioid Withdrawal

The last paragraph of this section:

There may be clinical settings, particularly the immediate postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. In these settings, consider use of an alternative, naloxone-containing product that can be titrated to effect and, where applicable, dosed according to the infant’s weight. *[see Use in Specific Populations (8.4)]*.

8.4 Pediatric Use

The final two paragraphs:

In settings such as in neonates with known or suspected exposure to maternal opioid use, where it may be preferable to avoid the abrupt precipitation of opioid withdrawal symptoms, consider use of an alternate naloxone-containing product that can be dosed according to weight and titrated to effect.

Also, in situations where the primary concern is for infants at risk for opioid overdose, consider whether the availability of alternate naloxone-containing products may be better suited than NARCAN Nasal Spray.

Regarding postmarket study requirements, the ability to study Narcan Nasal Spray in infants is fraught with ethical and technical challenges. It is not acceptable to study the pharmacokinetics of Narcan Nasal Spray in normal children. Naloxone is used in an emergency setting and its use cannot be predicted. As there is already approved therapy with naloxone for injection, and treatment cannot be delayed to discuss the study or obtain parental consent, there is no practical way to design a study to be conducted in the delivery room or an emergency room. The Applicant has agreed to provide the following enhanced pharmacovigilance:

- Submit both serious and non-serious outcomes as expedited reports within 15 days of receipt for the following:
 - All reports in patients less than one year of age
- Include a summary evaluation of each of these reports requested in the submission of the periodic reports for each reporting period, with an analysis of treatment failures and adverse events of airway obstruction, respiratory distress, or respiratory arrest; in addition to a summary of these events in the context of all similar events reported for Narcan Nasal Spray.

11. Other Relevant Regulatory Issues

From Dr. Lloyd's review:

Vicky Borders-Hemphill, PharmD, conducted the Division of Medication Error Prevention and Analysis (DMEPA) summative human factors study review. The human factors study was conducted in 53 participants who were representative of the intended user group, which consists of the general population of individuals 12 years and older and low literacy layusers who were untrained on the use of the device. Dr. Borders-Hemphill notes that “[o]f the 53 participants, 5 participants did not successfully complete one of the two critical tasks of inserting the nozzle into the nostril and pressing the plunger to release the dose in the nose:

- Two of the five participants administered the dose into the mouth of the overdose victim (mannequin). The Applicant's root cause analysis indicated that one of the participants used common sense rather than reading the IFU, and the other

participant thought that they only saw one opening on the mannequin, which was the mouth. None of the root causes were attributed to the product design or labeling.

- Two of the five participants did not press the plunger completely to release the dose. The Applicant's root cause analysis showed that these participants were confused by the setting of simulation, and attributed these failures to study artifacts.
- One of the five participants expelled the product into the air prior to inserting it into the nasal opening. The participant indicated that he was trying to test how hard to push the plunger prior to administering to the mannequin.

Dr. Borders-Hemphill concluded that "the human factors validation study report provides sufficient data to conclude that the product can be used safely and effectively by intended users for intended uses and environments" and recommended revised labeling based on this study.

Inspections of the clinical and analytical portions of the relative bioavailability study

Because the application is based on the results of the relative bioavailability study, a consult was issued to the Office of Study Integrity and Surveillance (OSIS) for inspection of the analytical portion of the pivotal relative bioavailability study (study 002) and the clinical portion of the study, arranged by OSIS with the Office of Regulatory Affairs (ORA). OSIS recommended that "the clinical and analytical data from study Naloxone-Phla-002 be accepted for Agency review." The final classification for both the clinical portion (Vince & Associates Clinical Research) and the analytical portion (b) (4) was VAI (voluntary action indicated).

The OSIS review noted two observations at the clinical site (Vince & Associates Clinical Research) and a Form FDA 483 was issued.

1. Observation: "An investigation was not conducted in accordance with the investigational plan."
2. Observation: "Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation."

Dr. Lloyd discusses these findings in detail in his review. For the first observation, there was failure to report a respiratory rate greater than 24 as an adverse event. Dr. Lloyd concurred with the OSIS conclusion that this was unlikely to have an impact on data reliability. It was also found that numerous pharmacokinetic samples that not placed in the freezer within the specified (b) (4) window. The analytical site, (b) (4) was requested to evaluate the stability of naloxone over conditions that mimicked the worst-case scenario for the samples at the clinical site. The results of this study were made available to the investigators over the course of this inspection, which demonstrated the stability of the samples. OSIS concluded that this issue "is unlikely to impact the integrity of the naloxone

concentration data.” The clinical pharmacology review team concurred with OSIS’s conclusion.

For the second observation, discrepancies were found between the reported protocol deviations and the source documents, specifically, post-dose discrepancies in the actual sampling times in the pharmacokinetic analysis for three subjects, at one post-dose time point each. Two of these subjects received a different formulation and the remaining had a one-minute deviation that Dr. Lloyd and Dr. Naraharisetti concluded would not affect the calculated pharmacokinetic parameters. In addition, there were discrepancies in some of the adverse event reporting, particularly, two subjects with adverse events related to nasal irritation (i.e., nasal edema and left nostril dryness with occasional bleeding) had nasal examinations recorded as normal, and two subjects with adverse events of nasal irritation had the nasal examination scores changed from normal to inflamed mucosa, no bleeding after the subjects had completed the study. It is possible that in the first two cases there were normal nasal examinations and it is unclear why the changes were made for the second two cases. Regardless, the overall risk associated with opioid overdose and the importance of the use of Narcan Nasal Spray in these settings outweighs the risk for nasal irritation.

There are no other unresolved relevant regulatory issues

12. Labeling

As noted in Dr. Lloyd’s review:

The proprietary name, Narcan nasal spray, was found acceptable following review by the Division of Medication Error Prevention and Analysis (DMEPA). DMEPA and the Office of Prescription Drug Promotion (OPDP) provided recommendations on the proposed labels and labeling. DMEPA noted that their proposed changes do not require an additional human factors validation study. The patient labeling team reviewed the patient package insert, instructions for use, and quick start guide and found them acceptable with their recommended changes. Refer to the individual reviews for more details.

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 made in the relevant sections of this review. However, two additional aspects of the proposed labeling warrant further discussion here:

1. The Applicant proposed

(b) (4)

(b) (4)
(u) (4)
The Applicant's proposal

2. Additionally, the Applicant proposes (b) (4)

I concur with Dr. Lloyd's analysis of the proposed labeling. Conceptually, all patients prescribed an opioid analgesic should have naloxone available to manage an opioid overdose. Also, I concur with the importance of having a second dose available in case of an error with the first dose or a failure to respond to the first dose.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval
- Risk Benefit Assessment

The pharmacokinetic profile from Narcan Nasal Spray demonstrates that a nasal spray can be formulated to result in efficacy comparable to the use of naloxone by intramuscular injection. In this case, the 4 mg dose of Narcan Nasal Spray provides naloxone concentrations ranging from 3.5-fold to 6-fold higher than a 0.4 mg intramuscular injection of 0.4 mg/mL naloxone solution. The 0.4 mg dose for the approved parental product represents a starting dose and is intended to be repeated up to a maximum of 10 mg if needed when attempting to reverse an known or suspected naloxone overdose. The benefit of using an incremental approach is that it may be possible to avoid precipitating an acute withdrawal syndrome in an opioid-tolerant patient, although this risk is outweighed if it means lessening the likelihood of reversing the overdose and reestablishing spontaneous respirations capable of providing adequate ventilation and oxygenation. Also, it is important to have at least one additional dose available for use in patients who fail to respond to the first dose.

- Recommendation for Postmarketing Risk Management Activities

The Applicant has agreed to the following request for special reporting of adverse events from use in pediatric patients less than one year of age. If any reports raise concerns about the safety, additional evaluation of the use in this age group will be considered.

- Submit both serious and non-serious outcomes as expedited reports within 15 days of receipt for the following:
 - All reports in patients less than one year of age
- Include a summary evaluation of each of these reports requested in the submission of the periodic reports for each reporting period, with an analysis of treatment failures and adverse events of airway obstruction, respiratory distress, or respiratory arrest; in addition to a summary of these events in the context of all similar events reported for Narcan Nasal Spray.
 - Recommendation for other Postmarketing Study Commitments

The following studies have been agreed to by the Applicant.

- 2990-1 Establish reliability requirements for the combination product Narcan Nasal Spray (naloxone hydrochloride), and complete testing which verifies the combination product reliability.
- 2990-2 Establish procedures for monitoring reports of failure of the combination product Narcan Nasal Spray (naloxone hydrochloride) to activate or failure of the combination product to deliver the full-labeled dose. Provide interim and final reports to the NDA, which contain a detailed analysis of reported device failures (including reported malfunctions that did, as well as did not result in patient harm), full event narratives of the failure and any subsequent adverse events, and the results of root cause analysis performed for the reported failure.
- 2990-3 Conduct an adequate leachable safety assessment for the (b) (4) plunger used in your container closure system. This assessment must include leachable data from long-term stability studies testing at least three batches (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. Using this information, conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. Submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 120 mcg/day for an acute indication, or be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples.
- 2990-4 Conduct a long-term stability evaluation placing at least three (3) manufactured lots of NARCAN Nasal Spray, 40 mg/mL, on long-term stability evaluation at the following temperatures:
- a. 2 to 8°C
 - b. 40°C/75% RH - to extend the time points out to 24 months

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/s/

SHARON H HERTZ
11/18/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208411Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Joshua M. Lloyd, MD
Subject	Cross-Discipline Team Leader Review
NDA	208411
Applicant	Adapt Pharma, Inc.
Date of Submission	July 20, 2015
PDUFA Goal Date	January 20, 2016
Proprietary Name / Established (USAN) names	Narcan nasal spray / Naloxone hydrochloride
Dosage forms / Strength	Intranasal spray / 40 mg/ml
Proposed Indication(s)	1. Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression 2. Intended for immediate administration as emergency therapy in settings where opioids may be present 3. Not a substitute for emergency medical care
Recommended:	Approval

1. Introduction

Adapt Pharma, Inc. ("Applicant"), submitted this new drug application (NDA) for Narcan (naloxone hydrochloride) nasal spray for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Narcan nasal spray is a single-use, drug-device combination product intended for use in the community. It is designed for use in non-healthcare settings by laypersons to rescue patients experiencing the life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention. The Applicant conducted the clinical development program under IND 114,704 in collaboration with the National Institutes for Drug Abuse (NIDA) and proposes to market Narcan nasal spray in one strength (i.e., 40 mg/ml) that delivers 0.1 ml (4 mg) in a single intranasal spray and is for use in patients of all ages, both adult and pediatric. The investigational new drug (IND) application was submitted by Lightlake Therapeutics, Inc. (also referred to as the "Applicant" throughout this review), on July 18, 2014, and the ownership of the IND was transferred to Adapt Pharma, Inc., on December 16, 2014. This IND was granted fast track designation on January 27, 2015, for the proposed indication.

The Applicant submitted bioavailability data to cross-reference their NDA for Narcan¹ (naloxone hydrochloride; NDA 16636), an injectable formulation of naloxone. Narcan was approved April 13, 1971, and is available for subcutaneous, intramuscular, and intravenous use

¹ The Narcan NDA was transferred from Endo Pharmaceuticals, Inc., to the Applicant effective May 26, 2015

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 is also indicated for diagnosis of suspected or known acute opioid overdose. The indication and usage section of the labeling further states that Narcan may be useful as an adjunctive agent to increase blood pressure in the management of septic shock. 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 manufactured by (b) (4) in the pivotal relative bioavailability study to create a scientific bridge to their NDA for Narcan to establish the safety and efficacy of Narcan nasal spray for the proposed indication. Although the Applicant owns the Narcan NDA, this NDA for Narcan nasal spray is relying on the published literature to support the safety and efficacy of the product in the pediatric population and, therefore, was submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

This NDA was accepted for rolling review and was granted priority review status upon submission of the final sections of the application reflecting the importance of this product from the public health perspective, as, currently, there are no approved intranasal naloxone products intended for use in the community.

Both Narcan nasal spray and Narcan contain naloxone, and the proposed population for Narcan nasal spray (i.e., known or suspected opioid overdose) is encompassed by the indicated population for Narcan. However, several important differences exist between Narcan nasal spray and Narcan. Narcan nasal spray represents a change in the route of administration from intravenous (IV), intramuscular (IM), or subcutaneous (SC) injection to intranasal (IN). Therefore, the Applicant evaluated the potential for local toxicity in the relative bioavailability studies. Narcan nasal spray also represents a change in the intended setting. Narcan is generally used in healthcare settings by healthcare professionals, whereas Narcan nasal spray is intended to be used in a community setting by laypersons. The Applicant submitted a human factors evaluation to support use in this different setting. Lastly, the proposed dosing for Narcan nasal spray represents a change in dosing regimen for pediatric patients. Narcan labeling recommends weight-based dosing in pediatric patients, whereas Narcan nasal spray contains a fixed dose of naloxone. This review will explore these issues in greater detail, in addition to confirming that Narcan 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. Background

Accidental or intentional overdose and death associated with the use, misuse, and abuse of illicit and/or 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 and in people who misuse or abuse opioids. Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that, if not immediately

treated, may lead to significant morbidity and mortality due to irreversible hypoxic injury. Naloxone is a nonselective opioid receptor antagonist, with the greatest affinity for the mu-opioid receptor that, if immediately administered, can reverse these life-threatening effects in an opioid overdose and prevent hypoxia-associated injury and death. However, there are limitations to the use of naloxone in this setting. The effects of some opioids, such as buprenorphine, may be difficult to antagonize. Larger doses of antagonist may be necessary than are available and the opioid overdose must be reversed before hypoxia results in irreversible injury. Also, it is important to realize that the duration of antagonists such as naloxone are generally shorter than the duration of action of most opioids. Therefore, even when an antagonist is available, it is not a substitute for seeking emergency medical help.

The US Department of Health and Human Services (HHS) has made addressing this public health crisis a top priority and has outlined a targeted initiative to do so that includes providing training and educational resources, increasing the use of naloxone, and expanding the use of medication-assisted treatment. The availability of an approved intranasal naloxone product intended for use in the community would contribute towards meeting these goals and is of great importance from a public health perspective.

Generic versions of Narcan are currently available; the approved Narcan labeling recommends initial doses of 0.4 mg to 2 mg for known or suspected opioid overdose in adults with repeat doses every two to three minutes up to a total of 10 mg. In children, initial doses of 0.01 mg/kg with repeat doses of 0.1 mg/kg are recommended. Additionally, Evzio, an injectable naloxone product that delivers 0.4 mg of naloxone HCl intramuscularly or subcutaneously intended for use in the community, was approved on April 3, 2014, and is available.

Naloxone has also been increasingly available in the community through a variety of public health programs, which have generally supplied an injectable formulation of naloxone (i.e., either a vial or syringe) along with a needle or mucosal atomizer device (MAD) to provide access to this life-saving medicine. The MAD allows for the injectable formulation to be delivered as an intranasal spray (currently, an off-label route of administration), typically from an injectable solution containing 2 mg of naloxone HCl in 2 ml of solution. The bioavailability of this off-label intranasal route of administration using an MAD may be less than the exposure following approved routes of administration for naloxone, based on reports in the literature, but there are also reports in the literature and from addiction treatment programs that naloxone administered this way has been successful in reversing opioid overdose. Therefore, the minimum effective dose of naloxone is unclear.

Evaluating the efficacy of a new formulation or route of administration of naloxone to establish an effective dose range presents significant logistical and ethical challenges, as already-approved naloxone-containing products are available for treatment of this life-threatening condition, which, if not immediately treated, could result in substantial morbidity and mortality. The Division has determined that it would not be ethical to deliver an experimental naloxone (i.e., through a novel formulation or via a novel route of administration) to an actual patient suffering from opioid overdose and potentially delay life-saving treatment with an already-approved naloxone product in the context of a clinical

efficacy study. Furthermore, intentionally administering enough opioid to actually create a clinically meaningful opioid overdose is not ethical.

Therefore, the Division has outlined a path for the clinical development of novel naloxone products, including those intended to be used in the community, which consists of demonstrating comparable or greater systemic exposure to naloxone with the new naloxone product, particularly in the early critical period after drug administration. This relative bioavailability study would be conducted in healthy volunteers, thus obviating the need to conduct a study in patients suffering from an opioid overdose. The necessary clinical development program was discussed with the Applicant at a Pre-IND meeting held May 24, 2012. It was further discussed that, although the proposed product represents a new route of administration, nonclinical studies to evaluate local toxicity would not be required given the clinical experience with intranasal naloxone, lack of any novel excipients, the acute use of the drug product, and the potentially life-saving indication, provided that the Applicant includes adequate clinical monitoring of local tissues in the relative bioavailability studies. A Pre-NDA meeting was held March 27, 2015.

3. CMC/Device

The Quality Assessment review consisted of the following disciplines: Drug Substance and Drug Product (Venkat Pavuluri, PhD), Process (Christina Capacci-Daniel, PhD and Edwin Jao, PhD), Microbiology (Christina Capacci-Daniel, PhD, and Erika Pfeiler, PhD), Facility (Christina Capacci-Daniel PhD and Grace McNally, PhD), Regulatory Business Process Manager (Steve Kinsley), Application Technical Lead (Julia Pinto, PhD), and CDRH OC Combination Products (Juandria Williams). CDRH was also consulted (Ryan McGowan and Rick Chapman). The information for the naloxone drug substance is referenced in DMF (b) (4) for which (b) (4) is the holder, and the information for the nasal spray device is referenced in DMF (b) (4) for which (b) (4) is the holder. Both DMFs were found to be adequate. The quality review team recommended approval for this NDA. The following is a summary of the quality review.

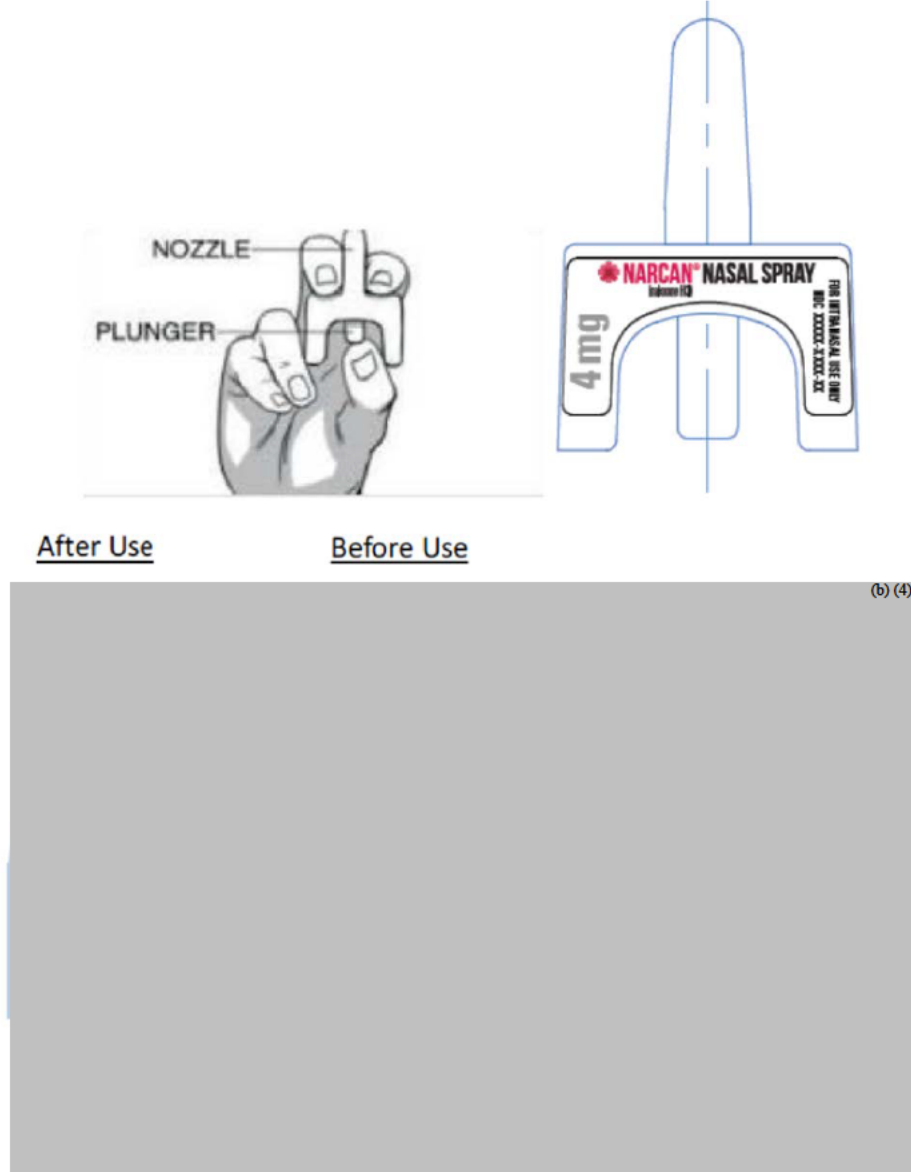
The quality review team noted that:

The naloxone API is supplied by (b) (4). The drug product is formulated in (b) (4) comprising the following excipients: sodium chloride, (b) (4) and benzalkonium chloride, in a concentration of 40 mg/ml. The container closure system is a glass vial with a (b) (4) stopper, which is then encased within a nasal actuator and container holder. The nasal spray device is by (b) (4), under DMF (b) (4), and has been reviewed by CDRH and OPQ, for use with the naloxone drug product. Each unit dose device, formulated to deliver one dose of naloxone, is placed within a blister package. Two units or blister packages are then stored per carton. Adequate data to assess the device delivery of the drug product and to assure the identity, strength, purity, and quality of the drug product is provided. The drug product is granted an expiry of 24 months, when stored at room

temperature. Further, the Office of Process and Facilities, has made an overall recommendation of adequate for all facilities related to this application.

Dr. Pavuluri noted that “the drug substance specifications include both USP and EP monograph specified tests and acceptance criteria (wherever the methods and acceptance criteria in the two compendia are different),” and found this to be adequate. He further noted that “[t]he drug substance complies with the USP monograph and USP <467> Residual Solvents” and found this to be acceptable. The drug product solution is presented in a 125 μ L (0.125 mL) (b) (4) glass vial (fulfills the requirements of USP) closed with a (b) (4) plunger (container closure system), which in turn is mounted into a unit-dose non-pressurized nasal spray device and container holder assembly. When the device is actuated (b) (4) and deliver a 100 μ L (0.1 mL) spray of the naloxone intranasal solution. There is no priming required before use and that the device can be used in any orientation.

Figure 1. Schematic Representations of the Narcan Nasal Spray Drug Product



Dr. Pavuluri found the drug product specifications to be adequate. Dr. Pavuluri noted that “[a]vailable stability data support [the] proposed expiration dating of 24 months from the date of manufacture of the drug product. [The Applicant] also commits to conduct stability studies on [an] additional three validation/commercial batches of the drug product, 40 mg / mL (4 mg / spray) post approval, stored at accelerated and long-term storage conditions and on one batch annually at 25°C/60 % RH as long as the drug product is manufactured ,” as is required.

Over the course of labeling negotiations, the Applicant proposed to allow excursions from the storage conditions to 4°C to 40°C. The CMC team held a teleconference with the Applicant on November, 16, 2015, and found the Applicant’s proposal acceptable, based on existing preliminary data, provided that the Applicant agree to a postmarketing commitment to test drug product batches on stability through the course of expiry at the excursion conditions of 4°C to 40°C.

Dr. Capacci-Daniel noted that the manufacturing process controls are adequate and that “there are no significant, outstanding manufacturing process risks that prevent approval of this application” and that “there are no significant, outstanding microbiological risks that prevent approval of this application.”

Dr. Capacci-Daniel found all of the facilities to be acceptable; however, she recommended post-approval inspections of several of the facilities (drug product and device).

The CDRH design review was conducted by Ryan McGowan, biomedical engineer. This review was conducted to evaluate the information submitted in this NDA that is intended to support the safety and functionality of the of the device constituent parts of the propose drug-device combination product. Mr. McGowan determined that “the device constituent parts of the combination product have been designed appropriately for the product’s intended use and essential performance requirements have been verified with a reasonable degree of certainty at a time period shortly after manufacture.” However, Mr. McGowan notes that the application contains inadequate information to demonstrate that the manufactured product is able to activate reliably after exposure to a variety of real-world conditions. There is a potential for under-dose or failure-to-dose events leading to undertreated, life-threatening CNS and respiratory depression as a consequence of a device failure under these conditions. Mr. McGowan recommends approval, from the device constituent design perspective, with postmarket requirements / commitments to verify combination product reliability. I concur with Mr. McGowan. Because this product should only be made available in a two-pack configuration, (b) (4) (refer to Section 12 below for additional discussion), of the impressive pharmacokinetic profile of this product, and of the importance of having an approved intranasal product available for use in the community, it is acceptable to approve this product with a postmarketing requirement to evaluate reliability of the product in a variety of conditions.

Mr. McGowan found the device-related product specifications acceptable with the exception of dose content uniformity, which allowed for relatively wide batch release specifications. This specification requires that (b) (4)

(b) (4)

Given the relatively wide safety margin with naloxone, there is little concern for the upper limits of these release specifications, particularly since Narcan is labeled with dosing recommendations up to a total of 10 mg of naloxone. In general, the greatest concern would be for releasing a batch that might not deliver an adequate dose of naloxone in an immediately life-threatening situation. However, given the pharmacokinetic profile of this product (refer to Section 5 below), which achieves much higher systemic exposures to naloxone than the approved comparator dose of naloxone (i.e., 0.4 mg IM), the lower limit of these specifications are also acceptable. Additionally, Narcan nasal spray should only be made available in a two-pack configuration, (b) (4) (refer to Section 12 below for additional discussion), ensuring that a second dose is available in the event of an inadequate response.

Vicky Borders-Hemphill, PharmD, conducted the Division of Medication Error Prevention and Analysis (DMEPA) summative human factors study review. The human factors study was conducted in 53 participants who were representative of the intended user group, which consists of the general population of individuals 12 years and older and low literacy layusers who were untrained on the use of the device. Dr. Borders-Hemphill notes that “[o]f the 53 participants, 5 participants did not successfully complete one of the two critical tasks of inserting the nozzle into the nostril and pressing the plunger to release the dose in the nose:

- Two of the five participants administered the dose into the mouth of the overdose victim (mannequin). The Applicant’s root cause analysis indicated that one of the participants used common sense rather than reading the IFU, and the other participant thought that they only saw one opening on the mannequin, which was the mouth. None of the root causes were attributed to the product design or labeling.
- Two of the five participants did not press the plunger completely to release the dose. The Applicant’s root cause analysis showed that these participants were confused by the setting of simulation, and attributed these failures to study artifacts.
- One of the five participants expelled the product into the air prior to inserting it into the nasal opening. The participant indicated that he was trying to test how hard to push the plunger prior to administering to the mannequin.

Dr. Borders-Hemphill concluded that “the human factors validation study report provides sufficient data to conclude that the product can be used safely and effectively by intended users for intended uses and environments” and recommended revised labeling based on this study.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by Newton Woo, PhD, with secondary concurrence by R. Daniel Mellon, PhD. The following is a summary of the nonclinical pharmacology/toxicology review.

The Applicant did not submit any new nonclinical studies to support this NDA and none were required. Dr. Woo concluded that “[t]he Applicant has provided adequate data to support the

safety of the drug substance, drug product, and drug product formulation.” There are no novel excipients in Narcan nasal spray. All of the excipients are listed in the FDA Inactive Ingredients Database (IID) and are present at lower levels than contained in several FDA-approved nasal drug products. The Applicant’s specifications for the drug substance comply with the requirements of the United States Pharmacopeia (USP) and European Pharmacopoeia (EP) monographs, based on a maximum daily dose of two sprays (8 mg of naloxone hydrochloride). Dr. Woo found the impurity specifications acceptable, including the specification for (b) (4) (not detected). Dr. Woo noted that the drug product specifications for the degradants were acceptable, including for (b) (4) (not detected).

Regarding the container-closure system, the Applicant provided data on extractables; however, the Applicant did not conduct a leachables assessment. The Applicant noted that leachables will be evaluated in long-term stability samples. The nonclinical review team concluded that “the absence of leachables data does not preclude marketing approval for the following reasons: 1) the (b) (4) plunger is used in other FDA-approved aqueous based nasal and injectable drug products; 2) analysis of water extracts did not identify any substances; 3) the Applicant has committed to monitor for leachables during stability; 4) most importantly, this product is indicated for an acute, single-use indication; and 5) the drug product is a potentially life-saving therapy.” Dr. Woo recommends approval with a postmarketing commitment (PMC) to complete the leachables assessment in addition to providing comments to the Applicant on the leachables assessment (see Section 13 below). I concur with the conclusions reached by the nonclinical reviewer, including that there are no nonclinical issues that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Suresh Naraharisetti, PhD, with secondary concurrence by Yun Xu, PhD. According to the clinical pharmacology team, this NDA is acceptable. The following is a summary of the findings from the clinical pharmacology review.

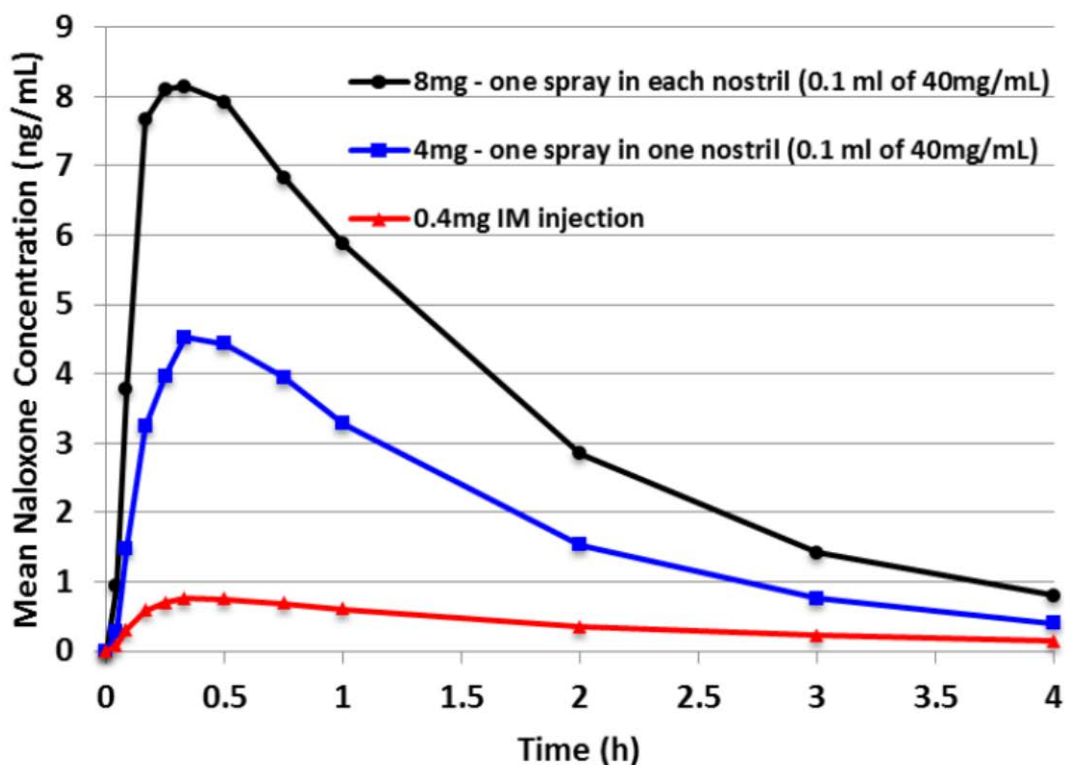
The Applicant conducted study Naloxone-Ph1a-002 (also referred to as study 002, in this review), a pivotal relative bioavailability study, in support of this application to establish a scientific bridge to their NDA for Narcan (NDA 16636) in order to establish the safety and efficacy of Narcan nasal spray.

Study 002 was an open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover study conducted in 30 adult male and female healthy volunteers in an inpatient setting to evaluate the pharmacokinetics of two doses of Narcan nasal spray (i.e., 4 mg [one spray in one nostril] and 8 mg [one spray in each nostril] in comparison to an approved generic version of naloxone given intramuscularly (i.e., 0.4 mg). Two doses of another formulation of intranasal naloxone that are not the to-be-marketed formulation were also evaluated in this study. Subjects were assigned to one of five sequences, with six subjects planned in each sequence. A four-day washout period separated the treatments. Narcan nasal spray was administered using an (b) (4) single-dose device (b) (4) with the subject in a fully supine position.

The left nostril was used for the 4-mg dose, and one spray was administered into each nostril for the 8-mg dose. Subjects were instructed not to breathe through the nose during administration of Narcan nasal spray and remained fully supine for approximately one hour post-dose. Intramuscular (IM) naloxone was administered as a 1-ml (i.e., 0.4 mg/ml) single injection into the gluteus maximus muscle using a 23-gauge needle.

Both one Narcan nasal spray in one nostril (i.e., 4-mg dose) and one Narcan nasal spray in each nostril (i.e., 8-mg dose) demonstrated much higher systemic exposure to naloxone, in terms of both AUC and C_{max} values, in comparison to the reference product. The naloxone plasma concentration-time profiles are shown in Figure 2. Narcan nasal spray exhibited a 5.5 -fold higher C_{max} and 4.7 -fold higher AUC_t from one spray in one nostril (4 mg total dose) and 11 -fold higher C_{max} and 8.9 -fold higher AUC_t from one spray in each nostril (8 mg total dose) compared to the reference, a single dose of naloxone 0.4 mg given via IM injection.

Figure 2. Mean Plasma Concentration-Time Profiles of Naloxone from 0 to 4 hours Following Intranasal and Intramuscular Naloxone Administration to Healthy Subjects (N = 30; n=29 for each treatment)



Source: Dr. Naraharisetti's review, pg. 3

Both Narcan nasal spray doses demonstrated higher naloxone concentrations than the reference product at all time points, as described in Table 1.

Table 1. Comparison of Mean Naloxone Concentrations between Intramuscular Naloxone and Two Doses of Narcan Nasal Spray from 2.5 to 60 Minutes Post Dose.

Time post-dose after naloxone drug product administration (minutes)	Mean Concentration (ng/mL) (% CV) N=29			Fold higher naloxone concentration:	Fold higher naloxone concentration:
	Reference	Test	Test		
	IM injection (0.4 mg)	One IN spray in one nostril (4mg)	One IN spray in each nostril (8mg)	One IN spray (4mg) Vs. IM injection (0.4 mg)	One IN spray in each nostril (8mg) Vs. IM injection (0.4mg)
2.5	0.079 (168)	0.28 (151)	0.93(131)	3.5	11.8
5	0.306 (108)	1.48 (117)	3.78 (105)	4.8	12.3
10	0.578 (55)	3.24 (67)	7.66 (68)	5.6	13.3
15	0.696 (46)	3.97 (56)	8.10 (44)	5.7	11.6
20	0.754 (36)	4.53 (50)	8.14 (31)	6.0	10.8
30	0.749 (25)	4.43 (43)	7.92 (25)	5.9	10.6
45	0.684 (25)	3.95 (41)	6.83 (24)	5.8	10.0
60	0.604 (24)	3.28 (37)	5.87 (23)	5.4	9.7

Source: Dr. Naraharisetti's review, pg. 4

Dr. Naraharisetti noted that “[t]he median naloxone Tmax after IN administration was not significantly different compared to the IM administration.” However, the Tmax for the IM route exhibited relatively high variability (i.e., range of 0.08 to 2.05 hours) compared to the IN route. Further, the IN route had slightly longer half-life of 2.1 hours compared to 1.2 hours for IM route.

I concur with the conclusions reached by the clinical pharmacology reviewer. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical- Efficacy

No new clinical efficacy studies were submitted in support of this application. The Applicant is cross-referencing their NDA for Narcan (naloxone hydrochloride, NDA 16636), which is approved for known or suspected opioid overdose, to establish the safety and efficacy of the proposed product.

8. Safety

There were no new safety studies submitted in support of this application. The Applicant is cross-referencing their NDA for Narcan (naloxone hydrochloride; NDA 16636) to establish the safety and efficacy of the proposed product. The relative bioavailability study

demonstrated that the naloxone levels achieved with Narcan nasal spray are approximately five times that of 0.4 mg naloxone given IM. This exposure is likely to fall well within the doses recommended in the approved Narcan labeling, which recommends up to a 2 mg initial dose and repeating the dose every two to three minutes up to a total dose of 10 mg.

Naloxone is generally administered in the setting of opioids, and many of the adverse events described in approved Narcan labeling may be attributable to the reversal of the effects of the opioid. Narcan labeling describes the potential for precipitation of opioid withdrawal in opioid-tolerant patients characterized by 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. In the neonate, opioid withdrawal may also include convulsions, excessive crying, and hyperactive reflexes.

Narcan labeling also notes that, in the postoperative setting, there have been postmarketing reports of hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs, which may have similar adverse cardiovascular effects. Excessive doses of naloxone hydrochloride in postoperative patients have resulted in significant reversal of analgesia and have caused agitation.

Because of the higher fixed dose of this product (i.e., 4 mg, which provide roughly 5 times the systemic exposure of a 0.4 mg IM dose), as compared to other naloxone-containing products intended for use in the community (e.g., Evzio), and the concern for precipitating adverse events related to the reversal of the opioid (i.e., in an inpatient postoperative population and in opioid-tolerant neonates), additional warning language is warranted to inform prescribers that:

In monitored settings, in situations where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms, consider use of an alternate naloxone-containing product that can be titrated to effect and, where applicable, dosed according to weight. These situations include the emergency treatment of opioid overdose, as manifested by respiratory and/or central nervous system depression in the immediate, inpatient postoperative period, particularly in patients with pre-existing cardiac disease, and in the postpartum period in neonates with known or suspected exposure to maternal opioid use.

Refer to the discussion under “Section 10 Pediatrics” regarding additionally addressing the potential for inducing neonatal opioid withdrawal.

Narcan labeling recommends dosing with naloxone for suspected opioid overdose with repeat dosing in adults up to 10 mg before questioning the diagnosis of opioid overdose. The risk of administering Narcan nasal spray to a patient who is not opioid-tolerant and whose symptoms are caused by an emergency other than opioid overdose is minimal given this wide safety margin. Because Narcan nasal spray can be administered in a very timely fashion and the

labeling recommends immediately seeking emergency medical attention after the first dose, it is unlikely that administering Narcan nasal spray to a patient suffering another emergency would significantly delay their definitive treatment.

The Applicant conducted two Phase 1 relative bioavailability studies in healthy volunteers, Naloxone-Ph1a-001 (also referred to as study 001, in this review) and Naloxone-Ph1a-002 (also referred to as study 002, in this review), comparing various intranasal (IN) formulations of naloxone to an approved injectable formulation of naloxone given via the intramuscular (IM) route. Because this NDA represents a change in the route of administration from the original Narcan NDA, the development program was required to evaluate the potential for local toxicity with this new route of administration. The Division determined that nonclinical studies to evaluate local toxicity would not be required, provided that the clinical studies included an assessment of nasal irritation (see discussion under Section 2). Both of the relative bioavailability studies collected safety data and included a formal assessment of nasal irritation. Only study 002 evaluated the to-be-marketed drug product.

Study 001

Study 001 was an open-label, randomized, 3-period, 3-treatment, 6-sequence, crossover, inpatient study conducted in 14 healthy adult volunteers to compare the pharmacokinetics of 2 doses of IN naloxone to IM naloxone and to evaluate safety. Subjects received a single 2 mg IN dose (one spray of 0.1 mL of a 10 mg/mL solution in each nostril), a single 4 mg IN dose (2 sprays of 0.1 mL of a 10mg/mL solution in each nostril), and a single 0.4 mg IM dose. The to-be-marketed formulation was not used in these studies, therefore, the results of this study are not emphasized in this review.

Study 002

Title: Phase 1, Pharmacokinetic Evaluation of Intranasal and Intramuscular Naloxone in Healthy Volunteers

Objectives:

- To determine the pharmacokinetics of four IN doses of naloxone compared to a 0.4 mg dose of IM naloxone to identify an appropriate IN dose that could achieve systemic exposure comparable to an approved parenteral dose
- To determine the pharmacokinetics of two different concentrations (20 mg/mL and 40 mg/mL) of IN naloxone.
- To determine the safety of IN naloxone, particularly with respect to nasal irritation (erythema, edema, and erosion).

Duration: 18 days inpatient; single-dose with 4-day washout between doses

Population: Healthy adult volunteers

- Inclusion criteria
 - Males and females 18 to 55 years of age
 - Provide written informed consent

- BMI ranging from 18 to 30 kg/m²
- Adequate venous access
- No clinically significant concurrent medical conditions determined by medical history, physical examination, clinical laboratory examination, vital signs, and 12-lead ECG
- Agree to use a reliable double-barrier method of birth control from the start of screening until one week after completing the study. Oral contraceptives are prohibited.
- Agree not to ingest alcohol, drinks containing xanthine >500 mg/day (e.g., cola, coffee, tea, etc.), or grapefruit/grapefruit juice or participate in strenuous exercise 72 hours prior to admission through the last blood draw of the study
- Exclusion criteria
 - Any IN conditions including abnormal nasal anatomy, nasal symptoms (i.e., blocked and/or runny nose, nasal polyps, etc.), or having a product sprayed into the nasal cavity prior to drug administration
 - Taking prescribed or over-the-counter medications, dietary supplements, herbal products, vitamins, or recent use of opioid analgesics for pain relief (within 14 days of last use of any of these products)
 - Positive urine drug test for alcohol, opioids, cocaine, amphetamine, methamphetamine, benzodiazepines, THC, barbiturates, or methadone at screening or admission
 - Previous or current opioid, alcohol, or other drug dependence (excluding nicotine and caffeine), based on medical history
 - Subject consumes greater than 20 cigarettes per day on average, in the month prior to screening, or would be unable to abstain from smoking (or use of any nicotine-containing substance) for at least one hour prior to and 2 hours after naloxone dosing.
 - On standard 12-lead ECG, a QTcF interval >440 msec for males and >450 msec for females
 - Significant acute or chronic medical disease
 - A likely need for concomitant treatment medication during the study
 - Donated or received blood or underwent plasma or platelet apheresis within the 60 days prior to Day -1
 - Female who is pregnant, breast feeding, or plans to become pregnant during the study period or within one week after naloxone administration
 - Positive test for HBsAg, HCVAb, or HIVAb at screening
 - Current or recent (within 7 days prior to screening) upper respiratory tract infection

Treatment:

- Naloxone 0.4 mg IM administered into the gluteus maximus muscle
- Naloxone 2 mg IN, one 0.1 mL spray of the 20 mg/ml formulation in one nostril

- Naloxone 4 mg IN, one 0.1 mL spray of the 20 mg/ml formulation in each of two nostrils
- Narcan nasal spray 4 mg (one 4 mg spray in one nostril)
- Narcan nasal spray 8 mg (one 4 mg spray in each of two nostrils)

IN naloxone was delivered using an (b) (4) single-dose device (b) (4) with the subject in a fully supine position. The subject remained fully supine for approximately one hour post-dose. Subjects were instructed not to breathe through the nose during administration of the nasal spray into the nose. The 40 mg/ml formulation using the (b) (4) device is the to-be-marketed product (i.e., Narcan nasal spray).

Design: This was an open-label, randomized, single-center, inpatient, 5-period, 5-treatment, 5-sequence, crossover study. Safety assessments included adverse events, physical examination, nasal passage examination, vital signs, laboratory tests (clinical chemistry, hematology, coagulation, urinalysis, and serum pregnancy test [females]), and electrocardiogram (ECG) (Table 2). Nasal irritation was evaluated by a trained observer at the time points listed in Table 2 on the following scale:

- Nasal Irritation Scale
 - 1 - Inflamed mucosa, no bleeding
 - 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

Table 2. Study 002 Time and Events Schedule

N = 30 subjects	Screening	Admission/ Baseline	Period 1	Washout			Period 2	Washout			Period 3	Washout			Period 4	Washout			Period 5	Dis-charge	Follow-Up
Study Day(s)	-21 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	+3 to 5 days
Informed Consent	X																				
Medical History	X	X																			
Demographics	X																				
Eligibility	X	X																			
Physical Examination	X	X																		X	X
Nasal Irritation Scoring	X	X	5X ^a	X			5X ^a	X			5X ^a	X			5X ^a	X			5X ^a	X	X
12-lead ECG	X	X	3X ^b				3X ^b				3X ^b				3X ^b				3X ^b	X	X
Vital Signs	X ^c	X ^c	5X ^d	X			5X ^d	X			5X ^d	X			5X ^d	X			5X ^d	X ^c	X ^c
Height, Weight, BMI	X																				
Clinical Chemistry & Coag ^e	X	X																		X	X
Hematology ^f	X	X																		X	X
Urinalysis ^g	X	X																		X	X
Serum Pregnancy test (females only)	X	X																			X
Drug/Alcohol Screen ^h	X	X																			X
HIV, Hepatitis B and C	X																				
PK Sample			16X				16X				16X				16X				16X		
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con. meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomize		X																			
IP Admin ⁱ			X				X				X				X				X		
Meals ^k		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

^a Nasal passage examination pre-dose, 5 minutes, 30 minutes, 60 minutes, 4 hours, and 24 hours post-dose.

^b 12-lead ECG approximately 60 minutes pre-dose, and 60 and 480 minutes post-dose.

^c Sitting blood pressure, heart rate, respiration rate, and temperature.

^d Sitting (5 minutes) blood pressure, heart rate, respiration rate, pre-dose and approximately 30 (supine position), 60, 120, and 480 minutes post-dose.

^e Chemistry parameters include: total protein, albumin, blood urea nitrogen, creatinine, alkaline phosphatase, ALT, AST, total bilirubin, glucose, sodium, potassium, chloride, CO₂, total cholesterol, and calcium. Coagulation parameters include PT and aPTT.

^f CBC with differentials and platelet count will be performed.

^g Urinalysis includes: pH, specific gravity, blood, ketones, nitrites, glucose, bilirubin, leukocyte esterase, protein.

^h Urine toxicology screen for alcohol, opioids, cocaine, amphetamine, methamphetamine, benzodiazepines, barbiturates, THC, or methadone.

ⁱ Pre-dose, 2.5, 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300, 360, 480, and 720 minutes post-dose.

^j Subjects will receive either a 0.4 mg IM dose of naloxone or a 2 mg (20 mg/mL), 4 mg (20 mg/mL), 4 mg (40 mg/mL) or a 8 mg (40 mg/mL) IN dose of naloxone depending upon the crossover randomization schedule.

^k Subjects will fast from midnight the day before naloxone dosing until one hour after dosing. Water will be provided *ad libitum*.

Source: Applicant, protocol for study 002, pp. 58-9

Study drug redosing and discontinuation criteria:

- Redosing criteria: vital signs had to be within the following limits before study treatment was administered:
 - Systolic blood pressure: 140 mmHg or less and greater than 90 mmHg
 - Diastolic blood pressure: 90 mmHg or less and greater than 55 mmHg
 - Heart rate: 100 beats per minute (bpm) or less and greater than 40 bpm
 - Respiratory rate: 20 respirations per minute (rpm) or less and greater than 8 rpm
- Discontinuation criteria:
 - Systolic blood pressure >180, diastolic blood pressure >110, respiratory rate >24 or <8
 - Significant arrhythmia defined as >6 beats of supraventricular tachycardia or ≥3 beats of ventricular tachycardia (study drug was discontinued for a clinically significant abnormal ECG at any time after clinic admission)
 - QTcF interval >500 msec
 - Reported significant nausea or abdominal pain

- Reported significant chest pain or dyspnea
- Subject confusion, seizures or seizure like behavior, agitation or inability to cooperate
- Subject requests to leave the experiment or is unwilling or unable to cooperate in carrying out the assigned protocol procedures

Primary endpoint: Pharmacokinetic

Secondary endpoints: Adverse events, vital signs (heart rate, sitting blood pressure, and respiratory rate), ECG, clinical laboratory changes, and nasal irritation (erythema, edema, and erosion)

Results

This section will focus on the results of study 002 because this is the only study that employed the to-be-marketed formulation. However, the results from study 001 did not identify any specific safety concerns for those other formulations of IN naloxone (i.e., no deaths, serious adverse events, or discontinuations due to adverse events; limited number of mild adverse events, none of which suggest significant local toxicity with IN naloxone).

Extent of exposure:

In study 002, there were a total of 87 single exposures of Narcan nasal spray to a nostril (Table 3). Thirty unique subjects received Narcan nasal spray, including 28 subjects who received both 4 mg in one nostril and 4 mg in each nostril (8 mg total dose), 1 subject who received 4 mg in one nostril only (subject was discontinued due to an adverse event), and 1 subject who received 4 mg in each nostril (8 mg total dose) but not 4 mg in one nostril (discontinued at the subject's request), as summarized in Table 4. The extent of exposure and nasal irritation monitoring are adequate to evaluate the potential for local toxicity.

Table 3. Overall Extent of Exposure, Studies 001 and 002.

Doses	001 ^{a,b} # of Subjects	002 ^{a,b} # of Subjects	Total # of Exposures
2 mg IN Naloxone (one 0.1 mL spray of 20 mg/mL formulation in one nostril)	-	29	43 (2 mg IN)
2 mg IN Naloxone (one spray of 20 mg/mL formulation in each nostril)	14	-	
4 mg IN Naloxone (two sprays of 20 mg/mL formulation in each nostril)	14	-	72 (4 mg IN)
4 mg IN Naloxone (one 0.1 mL spray of 20 mg/mL formulation in each nostril)	-	29	
4 mg IN Naloxone (one 0.1 mL spray of 40 mg/mL formulation in one nostril)	-	29	
8 mg IN Naloxone (one 0.1 mL spray of 40 mg/mL formulation in each nostril)	-	29	29 (8 mg IN)
0.4 mg IM Naloxone (1 mL of a 0.4 mg/mL commercial formulation)	14	29	43 (0.4 mg IM)

^a Study number begins with Naloxone-Ph1a

^b There was a 4-day washout period between doses.

Source: Applicant, summary of clinical safety, pg. 7

Subject disposition:

Subject disposition is summarized in Table 4. Thirty subjects were randomized with 28 subjects receiving all 5 treatments. Two subjects discontinued prior to completing the inpatient treatment period (one discontinuation due to an adverse event and one discontinuation due to the subject's request). Twenty-six subjects completed the follow-up visit.

Table 4. Subject Disposition, Study 002.

	Naloxone Administration Sequence					
	I	II	III	IV	V	Total
Randomized Participants	6	6	6	6	6	30
Discharged for safety reasons	-	-	1(a)	-	-	1
Withdrew before completing	-	1(b)	-	-	-	1
Completers	6	5	5	6	6	28
Underwent follow-up	6	4	5	5	6	26

a: Participant 2028 received only Narcan nasal spray 4 mg in one nostril

b: Participant 2046 received all treatments except Narcan nasal spray 4 mg in one nostril

Source: Applicant, study 002 clinical study report, pg. 32

Demographics and baseline characteristics:

Subjects ranged in age from 22 to 55 years, and the study population was predominantly male and African American (Table 5).

Table 5. Demographics and Baseline Characteristics, Study 002.

Label	Total (N=30)
Age (years)	
Mean	35.9
Standard Deviation	9.6
Minimum	22.0
Maximum	55.0
Weight (kg)	
Mean	80.1
Standard Deviation	13.4
Minimum	56.0
Maximum	102.0
Height (cm)	
Mean	173.3
Standard Deviation	9.5
Minimum	157.0
Maximum	190.0
BMI (kg/m²)	
Mean	26.5
Standard Deviation	2.6
Minimum	19.6
Maximum	29.8
Gender	
Female	12 (40.0%)
Male	18 (60.0%)
Race	
Black Or African American	23 (76.7%)
White	7 (23.3%)
Ethnicity	
Hispanic Or Latino	2 (6.7%)
Not Hispanic Or Latino	28 (93.3%)

Source: Applicant, study 002 clinical study report, pg. 32

Safety results:

All thirty subjects received at least one dose of study medication and were included in the safety population. There were no deaths or serious adverse events. One subject discontinued due to an adverse event (AE). This subject was a 26 year-old male with a history of smoking who was discontinued 4 days after receiving Narcan nasal spray 4 mg (one spray in one nostril). The subject had a blood pressure reading that did not meet redosing criteria and was discontinued by the investigator. The subject had the following blood pressure readings: 137/73 mmHg (screening), 144/73 mmHg (baseline), 138/81 mmHg (5 minutes pre-dose),

134/76 mmHg (30 minutes post-dose), 140/72 mmHg (60 minutes post-dose), 144/85 and 147/93 mmHg (120 minutes post-dose), 153/85 and 150/83 mmHg (480 minutes post-dose), and 147/87 and 160/84 mmHg (Day 2). Prior to the next scheduled dosing (Day 5), the subject's blood pressure was 141/80 and 144/86 mmHg. He was subsequently discontinued as he did not meet redosing criteria. This subject appears to have hypertensive issues at baseline, and it is unclear what role the study medication may have played in this case.

There were 27 adverse events (AEs) reported by 17 subjects. All AEs were considered mild in severity except for the one subject who experienced a moderate increase in blood pressure that lead to discontinuation. Table 6 lists all AEs that occurred in study 002. The list of AEs for a particular treatment includes all AEs recorded beginning with the administration of that treatment until the next treatment administration in the sequence. The Narcan nasal spray groups (40 mg/ml formulation) are highlighted in yellow in the table. AEs reported for subjects in the Narcan nasal spray groups included increased blood pressure, musculoskeletal pain, headache, and xeroderma, in addition to AEs indicative of local nasal irritation, including nasal dryness, nasal edema, nasal congestion, and nasal inflammation. The IM naloxone comparator arm reported nausea, dizziness, and headache.

Table 6. All Adverse Events, Treatment Period, Study 002.

MedDRA SOC	MedDRA PT	0.4 mg IM n=29	2 mg IN (one spray of 20 mg/ml) n=29	4 mg IN (two sprays of 20 mg/ml) n=29	4 mg IN (one spray of 40 mg/ml) n=29	8 mg IN (two sprays of 40 mg/ml) n=29
Cardiac and vascular investigations (excluding enzyme tests)	Blood pressure increased	0	0	0	1 (3.4%)	0
Gastrointestinal disorders	Constipation			1 (3.4%)		
	Nausea	1 (3.4%)				
	Toothache		1 (3.4%)			
Musculoskeletal and connective tissue disorders	Muscle spasms			1 (3.4%)		
	Musculoskeletal pain					1 (3.4%)
Nervous system disorders	Dizziness	1 (3.4%)				
	Headache	1 (3.4%)				1 (3.4%)
Respiratory, thoracic, and mediastinal disorders	Nasal dryness				1 (3.4%)	
	Nasal edema		4 (14%)		3 (10%)	1 (3.4%)
	Nasal congestion					1 (3.4%)
	Nasal inflammation		4 (14%)	1 (3.4%)	1 (3.4%)	
	Rhinalgia		1 (3.4%)			
Skin and subcutaneous tissue disorders	Xeroderma				1 (3.4%)	

Source: Reviewer, adapted from Applicant's Table 7, summary of clinical safety, pg. 14

The results of the nasal irritation exam are detailed in Table 7. The majority of subjects were found to have no irritation. Erosion was not observed in any subjects. No subject was scored higher than a "1" on the nasal irritation scale; all findings listed in Table 7 below were scored as a "1" on that scale.

Table 7. Nasal Irritation, Study 002.

Table 12.2.5-1. Nasal Irritation, Study Naloxone-Ph1a-002												
Scheduled Assessment	Treatment											
	2 mg (20 mg/mL, one 0.1 mL spray) N=29			4 mg (20 mg/mL, two 0.1 mL sprays) N=29			4 mg (40 mg/mL, one 0.1 mL spray) N=29			8 mg (40 mg/mL, two 0.1 mL sprays) N=29		
	Erythema	Edema	Erosion	Erythema	Edema	Erosion	Erythema	Edema	Erosion	Erythema	Edema	Erosion
Predose	1 (3.4%) ^a	1 (3.4%)	0	0	0	0	0	1 (3.4%)	0	0	0	0
5 min	0	3 (10.3%)	0	0	0	0	1 (3.4%)	0	0	0	0	0
30 min	0	3 (10.3%)	0	0	0	0	1 (3.4%)	0	0	0	0	0
60 min	0	1 (3.4%)	0	0	0	0	0	0	0	0	1 (3.4%)	0
4 hr	0	2 (6.9%)	0	0	0	0	0	1 (3.4%)	0	0	0	0
24 hr	2 (6.9%)	2 (6.9%)	0	1 (3.4%)	0	0	0	1 (3.4%)	0	0	0	0
Number (%) of Participants Observed with Nasal Irritation Symptoms												
Total	3 (10%)	5 (17%)	0	1 (3.4%)	0	0	1 (3.4%)	3 (10.0%)	0	0	1 (3.4%)	0

a: Number of participants (%)

Source: Applicant, study 002 clinical study report, pg. 68

The adverse event profile demonstrated the potential for Narcan nasal spray to result in mild local irritation. There is no question that this is an acceptable risk given the potentially life-saving benefits of this medication; however, the potential for local irritation will be communicated in labeling.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not held for this application.

10. Pediatrics

Narcan is approved for use in the entire pediatric age range. In contrast to adults, approved labeling recommends weight-based dosing for known or suspected opioid overdose in children. The Narcan package insert contains the following pediatric labeling:

Usage in Children

Opioid Overdose—Known or Suspected:

The usual initial dose in children is 0.01 mg/kg body weight given IV. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an IV route of administration is not available, naloxone may be administered IM or SC in divided doses. If necessary, naloxone hydrochloride injection can be diluted with sterile water for injection.

Because Narcan nasal spray represents a change in dosing regimen (a fixed 4-mg dose) and route of administration (intranasal) for naloxone, the Applicant is required to conduct a pediatric assessment under the Pediatric Research Equity Act (PREA). Efficacy studies are not feasible in pediatric patients in the same way they are not feasible in adults. However,

unlike in adults, pediatric pharmacokinetic studies in healthy children are not feasible because of limits on the ability to conduct studies in normal, healthy children where the study involves more than minimal risk. Therefore, the Applicant was required to support the safety and efficacy of Narcan nasal spray in pediatrics, based on a review of available information, including the published literature, clinical practice guidelines, and the approved labeling for Narcan. This 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
- Justification for the proposed dosing volume in all pediatric patients, including neonates
- Justification for why the absorption of drugs through the nasal mucosa will not be different in pediatric patients, including neonates, compared to adults
- A device (e.g., nasal tip) that can appropriately deliver the correct volume to all pediatric patients, including neonates

The Applicant received an agreed pediatric study plan (PSP) on June 22, 2015, which included a plan to submit the required pediatric assessment with the NDA. The Division of Pediatric and Maternal Health (DPMH) was consulted to evaluate the adequacy of the pediatric assessment to support approval in the full pediatric age range and the proposed labeling.

DPMH recommended “approval for the proposed indication for pediatric patients from birth to under age 17 years for emergency treatment of known or suspected opioid overdose until emergency medical services can be provided by trained professionals,” provided that “DAAAP is satisfied that IN delivery with the proposed unit dose device will result in absorption of a minimally effective dose in pediatric patients of all ages.”

DPMH raised concerns in their review about the safety of the proposed product as it relates to IN drug delivery. Specifically, DPMH requested DAAAP to confirm that the actuator tip may be properly positioned and, based on concerns of differences in nasal morphology, can deliver a minimally effective dose in pediatric patients under five years of age. Further, given the fixed dose, DPMH raised concerns that the 4-mg dose could deliver a dose approximately 100-fold higher than what is recommended in Narcan labeling if the full dose is systemically absorbed. DPMH raised additional concerns for the potential to induce respiratory distress with intranasal instrumentation in the youngest patients because of obligate nasal breathing.

Therefore, DPMH recommended a postmarketing requirement (PMR) and a postmarketing commitment (PMC) to, respectively, capture any treatment failures or serious AEs of airway obstruction, respiratory distress, or respiratory arrest in pediatric patients under one year of age and evaluate the pharmacokinetic profile of this product in patients under five years of age.

This application was discussed at a meeting of the Pediatric Review Committee (PeRC) on November 4, 2015, where the above PMC and PMR were initially discussed.

Narcan nasal spray is intended to address community-based treatment of opioid overdose, and it is vitally important that laypersons, who will be administering the product, do not have to

make complex medical decisions, such as determining a weight-based dose or having to decide between different doses for different age groups. The caregiver must seek definitive medical treatment on the patient's behalf after administering Narcan nasal spray in this treatment setting. Pediatric use of Narcan nasal spray in the **youngest** age ranges must be considered in the context of the different clinical scenarios where naloxone may be used in that population:

- Otherwise healthy children may be accidentally exposed to an opioid that is available in their environment resulting in life-threatening CNS and respiratory depression that requires naloxone.
- A pediatric patient who is taking a prescribed opioid for medical reasons may accidentally overdose on that opioid requiring naloxone. Use of naloxone in this population may result in signs and symptoms of opioid withdrawal if the patient is opioid-dependent, and this possibility would depend on the duration of prior opioid exposure.
- Naloxone may be required for neonates in the delivery room who present with respiratory depression at the time of birth due to maternal exposure to opioid, and these neonates may or may not be opioid-dependent depending on the duration of prior exposure to maternal opioids.
- Opioid-dependent babies born to mothers on medication-assisted treatment or who are illicitly using opioids may be treated with a gradual opioid taper at home in order to prevent life-threatening opioid withdrawal and may be at risk for opioid overdose.

Additional considerations in this treatment setting include that naloxone prescribed for use in the community may ultimately be administered to a person other than the recipient of the prescription because it cannot be known in advance who will overdose on an opioid. It is vitally important for Narcan nasal spray to be available for an accidental opioid ingestion in a child who may not have been the person for whom the prescription was written. Because of the wide safety margin for naloxone, particularly in non-opioid-dependent patients in a non-hospital setting, and that the dose of naloxone delivered from Narcan nasal spray, based on the pharmacokinetic study conducted in adults, is relatively high compared to what is recommended in the approved Narcan labeling for the youngest pediatric patients, there is a reasonable expectation that an effective dose of naloxone will be systemically available to reverse the life-threatening effects of the opioid in the youngest patients. Narcan nasal spray results in a systemic exposure to naloxone that is approximately 5 times that of the 0.4 mg IM dose. Evzio, which delivers a 0.4 mg IM dose, is approved in pediatric patients down to birth. Although the nasal tip may not fit in the nostrils of all pediatric patients, the opening through which the medication is sprayed is small enough to deliver the medication into the nose, if positioned properly.

In situations where a younger child is being considered for a prescription for naloxone to be used in the community to address the risk for accidental exposure or in cases where there is concern for inducing potentially life-threatening withdrawal, alternative products may be more appropriate. Additionally, in supervised medical settings, such as in the delivery room, emergency room, or inpatient unit, a weight-based naloxone dose that is amenable to titration is more appropriate.

The benefits of having this product available for those pediatric patients who may be accidentally exposed to an opioid resulting in life-threatening CNS and respiratory depression far outweighs the risks in this setting. Labeling must clearly describe which pediatric patients may not be the most suitable for this product so that the prescriber can make an informed decision as to which naloxone product to prescribe in these settings. I conclude that Narcan nasal spray should be approved for the full pediatric age range without the proposed PMR and PMC.

The concerns that DPMH raised resulting in their recommendations for a PMR could be addressed through enhanced pharmacovigilance, which should be considered to capture any treatment failures or serious AEs of airway obstruction, respiratory distress, or respiratory arrest in pediatric patients under one year of age. However, the Division has determined that, after extensive internal discussion, the proposed PMC to assess the pharmacokinetics in patients less than five years of age poses significant feasibility and ethical challenges because, in settings where this study could potentially be conducted (i.e., inpatient-type settings), another more appropriate naloxone therapy would be available (i.e., weight-based product), and, therefore, it would not be ethical to use a potentially suboptimal product for that setting in a clinical study. The value of this product in the community for the youngest pediatric patients will be clearly communicated in labeling, and its value does not necessarily fully extend to all community-based clinical scenarios or healthcare settings.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

Inspections of the clinical and analytical portions of the relative bioavailability study

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of the pivotal relative bioavailability study (study 002) and arranged an inspection of the clinical portion of the study with the Office of Regulatory Affairs (ORA). OSIS recommended that “the clinical and analytical data from study Naloxone-Phla-002 be accepted for Agency review.” The final classification for both the clinical portion (Vince & Associates Clinical Research) and the analytical portion (b) (4) was VAI (voluntary action indicated).

The OSIS review noted two observations at the clinical site (Vince & Associates Clinical Research) and a Form FDA 483 was issued.

1. Observation: “An investigation was not conducted in accordance with the investigational plan.”
 - The first issue involved one subject who developed a respiratory rate of 25 per minute at the 30-minute post-dosing time point. The protocol specified that subjects be discontinued for a respiratory rate of less than 8 or greater than 24 and did not allow for repeat measurements. However, the source document designed by the study site allows for repeated measurements, per the study site’s Standard Operating Procedure (SOP). A study sub-investigator was called to assess the

subject. The sub-investigator repeated the vital signs assessment and recorded a respiratory rate of 24 per minute. The finding was considered not clinically significant by the sub-investigator and the subject was allowed to continue in the study. The out-of-range respiratory rate was not documented as an adverse event (AE). The OSIS review noted that “[a]lthough the above observation is not likely to impact the study outcome, the DAAAP medical reviewer should evaluate the impact of this unreported adverse event (AE) on the safety evaluation of the investigational product.”

Adverse events are generally recorded by the investigator(s) at the clinical study site, based on a clinical evaluation of a patient or subject. Therefore, it is common that, in the context of clinical studies, not all out-of-range vital signs are coded as adverse events. In this case, I agree that the OSIS finding described above is unlikely to impact the safety evaluation of this drug, particularly since the finding of safety for Narcan nasal spray is primarily resting on the Applicant cross-referencing their NDA for Narcan injection.

- The second issue involved numerous pharmacokinetic samples that were late to the freezer (i.e., LTF; not placed in the (b) (4) °C freezer within (b) (4)). The failure to place serum samples in the freezer within (b) (4) was not documented on the site's protocol deviation log, nor were any LTF-related occurrences reported as protocol deviations.

To address this issue and to assess the integrity of LTF samples, the analytical site, (b) (4) was requested to evaluate the stability of naloxone over conditions that mimicked the worst-case scenario for the samples at the clinical site. The results of this study were made available to the investigators over the course of this inspection, which demonstrated the stability of the samples. OSIS concluded that this issue “is unlikely to impact the integrity of the naloxone concentration data.” The clinical pharmacology review team concurred with OSIS’s conclusion.

2. Observation: “Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.”

- The first issue involved discrepancies between the reported protocol deviations and the source documents. Specifically, the protocol deviations submitted to the Agency do not accurately represent the information from the pharmacokinetic Specimen Processing Log. OSIS determined that there were post-dose discrepancies in the actual sampling times in the pharmacokinetic analysis for three subjects, at one post-dose time point each. OSIS noted that “[t]his observation is unlikely to impact the outcome of the study.” However, OSIS requested that the clinical pharmacology reviewer include the actual sampling times in their pharmacokinetic analysis for these three subjects. The clinical pharmacology reviewer noted that two of the deviations were in subjects who received the 20 mg/ml strength, and, therefore, these two deviations can be

disregarded. The third subject had a one minute deviation at the 5-minute post-dose time point. The clinical pharmacology reviewer concluded that “this one minute deviation at [the] 5 minute time point in one subject would not affect the calculated [pharmacokinetic] parameters [or] conclusion for the study,” and I concur with that assessment.

- The second issue involved adverse event information not corresponding to applicable source documentation.

Two subjects reported adverse events related to nasal irritation (i.e., nasal edema and left nostril dryness with occasional bleeding); however, those subjects had corresponding nasal examinations recorded as normal (i.e., “0” on the nasal irritation scoring scale). Physical exam finding do not always correlate with subjective reports.

Two additional subjects reported adverse events related to nasal irritation and also had corresponding nasal examinations recorded as normal. However, these subjects had their corresponding nasal examination score(s) changed to “1” (inflamed mucosa, no bleeding) at a later time or date, in some cases over a month later.

For all of these cases, the same sub-investigator was involved (i.e., identified as “LDV”). These findings do not impact the safety evaluation of the investigational product. The finding of safety for Narcan nasal spray is primarily resting on the Applicant cross-referencing their NDA for Narcan injection. We are relying on this study to provide a qualitative assessment of the potential for local nasal irritation, and this study did demonstrate that Narcan nasal spray has the potential to cause mild local irritation. This conclusion is unchanged by these inspectional findings. Further, it is unlikely that the sub-investigator missed a serious finding on nasal examination, and the issue appears to be with the more clinically subtle aspects of the exam (i.e., “0” versus a “1”). However, these findings do raise concerns over the adequacy of the training for the clinical nasal examination.

Financial disclosures

The Applicant certified that the investigator did not have reportable financial disclosures.

505(b)(2) committee

This application was presented at a meeting of the 505(b)(2) committee on October 26, 2015, and it was cleared for action from their perspective. The 505(b)(2) committee recommended that an approval action be coordinated with the Exclusivity Board/Office of Regulatory Policy (ORP), as they may wish to include a memorandum to the record regarding the potential for exclusivity attached to other naloxone-containing products to block the approval of this NDA. A memorandum from ORP is pending at the time of this writing,

12. Labeling

The proprietary name, Narcan nasal spray, was found acceptable following review by the Division of Medication Error Prevention and Analysis (DMEPA). DMEPA and the Office of Prescription Drug Promotion (OPDP) provided recommendations on the proposed labels and labeling. DMEPA noted that their proposed changes do not require an additional human factors validation study. The patient labeling team reviewed the patient package insert, instructions for use, and quick start guide and found them acceptable with their recommended changes. Refer to the individual reviews for more details.

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. However, two additional aspects of the proposed labeling warrant further discussion here:

1. The Applicant proposed

(b) (4)

2. Additionally, the Applicant proposes

(b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant established the safety and efficacy of the naloxone contained in Narcan nasal spray by conducting a relative bioavailability study to bridge to their NDA for Narcan (NDA 16636). This study compared two doses of Narcan nasal spray to an approved generic injectable naloxone product and demonstrated that the systemic exposure to naloxone was much higher than that of an initial approved dose of naloxone for injection (i.e., 0.4 mg IM) at all measured time points. Therefore, the Applicant successfully met the pharmacokinetic standard outlined by the Division, which was required to ensure that Narcan nasal spray will deliver an effective dose of naloxone in a timely fashion. This is particularly important in the early time points where it is critical to provide adequate exposure to naloxone given the grave consequences of under treating an opioid overdose.

The application supported the change in route of administration by evaluating the potential for local toxicity in the relative bioavailability study, the change in intended treatment setting (i.e., from use in a healthcare setting by health professionals to use in a community setting by laypersons) by conducting a human factors study, and the change in dosing regimen for pediatric patients (i.e., from weight-based dosing to a fixed dose) by providing a pediatric assessment with support from the published literature.

This product would be the first approved intranasal naloxone product. It is intended for use in the community and will provide an important alternative to other approved naloxone products, which require a needle for drug administration. The risks discussed in this review are far outweighed by the potential benefits of this potentially life-saving medication. Therefore, I recommend approval for adults and the full range of pediatric patients in the proposed indication with the labeling recommendations described throughout this review.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

Postmarketing Requirements:

1. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability as described in detail below:
 - a. Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as $R(t) = x\%$, where t = time and $x\%$ = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a

population of devices to meet essential performance requirements after preconditioning to elements outlined within c, below. The reliability requirements should be verified with a high degree of statistical confidence.

- b. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.
- c. Perform a test to verify the reliability requirements specified above.

Devices assessed within the reliability test should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete.

- Shipping
- Aging
- Storage orientation and conditions
- Vibration handling
- Shock handling (e.g., resistance to random impacts, such as being dropped)

Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however, you should provide rationale supporting the final circumstances of activation chosen.

- Activation orientation
 - Environmental temperature
2. Establish procedures for monitoring reports of failure of the combination product to activate or failure of the combination product to deliver the full labeled dose. Provide annual updates to the NDA record, which contain a detailed analysis of reported device failures (including reported malfunctions that did not result in patient harm), full event narratives, and the results of root cause analysis performed for the reported failure.

Postmarketing Commitments:

1. Conduct and submit an adequate leachable safety assessment for your drug product and container closure system. This assessment must include leachable data from long-term stability studies taking into consideration the proposed shelf-life to determine if the specified extractables also leach into the drug product over time, and a toxicological risk assessment justifying the safety of the leachables taking into consideration the maximum daily dose of the identified materials for this drug product.

2. A postmarketing commitment to test drug product batches on stability through the course of expiry at the excursion conditions of 4°C to 40°C. (final language pending at the time of this writing)
- Recommended Comments to Applicant

Additional Comments for the Leachables Assessment:

1. The leachable compounds you propose to evaluate in your leachables assessment appear appropriate.
2. In your leachables assessment, evaluate at least three batches of your drug product over the course of your stability studies at multiple timepoints during the proposed shelf-life of your product.
3. Submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 120 mcg/day for this acute indication, or be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.
 - Published literature to support the safety of a leachable rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your container closure system.
 - Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the leachable.

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

/s/

JOSHUA M LLOYD
11/18/2015

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NARCAN NASAL SPRAY safely and effectively. See full prescribing information for NARCAN[®] NASAL SPRAY.

NARCAN[®] (naloxone hydrochloride) nasal spray
Initial U.S. Approval: 1971

-----INDICATIONS AND USAGE-----

NARCAN Nasal Spray is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. (1)

NARCAN Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present. (1)

NARCAN Nasal Spray is not a substitute for emergency medical care. (1)

-----DOSAGE AND ADMINISTRATION-----

- NARCAN Nasal Spray is for intranasal use only. (2.1)
- Seek emergency medical care immediately after use. (2.1)
- Administer a single spray of NARCAN Nasal Spray to adults or pediatric patients intranasally into one nostril. (2.2)
- Administer additional doses of NARCAN Nasal Spray, using a new nasal spray with each dose, if the patient does not respond or responds and then relapses into respiratory depression, additional doses of NARCAN Nasal Spray may be given every 2 to 3 minutes until emergency medical assistance arrives. (2.2)
- Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance. (2.2)

-----DOSAGE FORMS AND STRENGTHS-----

Nasal spray: 4 mg of naloxone hydrochloride in 0.1 mL (3)

-----CONTRAINDICATIONS-----

Hypersensitivity to naloxone hydrochloride (4)

-----WARNINGS AND PRECAUTIONS-----

- Risk of Recurrent Respiratory and CNS Depression: Due to the duration of action of naloxone relative to the opioid, keep patient under continued surveillance and administer

repeat doses of naloxone using a new nasal spray with each dose, as necessary, while awaiting emergency medical assistance. (5.1)

- Risk of Limited Efficacy with Partial Agonists or Mixed Agonists/Antagonists: Reversal of respiratory depression caused by partial agonists or mixed agonists/antagonists, such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses may be required. (5.2)
- Precipitation of Severe Opioid Withdrawal: Use in patients who are opioid dependent may precipitate opioid withdrawal. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. Monitor for the development of opioid withdrawal. (5.3)
- Risk of Cardiovascular (CV) Effects: Abrupt postoperative reversal of opioid depression may result in adverse CV effects. These events have primarily occurred in patients who had pre-existing CV disorders or received other drugs that may have similar adverse CV effects. Monitor these patients closely in an appropriate healthcare setting after use of naloxone hydrochloride. (5.3)

-----ADVERSE REACTIONS-----

The following adverse reactions were observed in a NARCAN Nasal Spray clinical study: increased blood pressure, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, and nasal inflammation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Adapt Pharma, Inc. at 1-844-4NARCAN (1-844-462-7226) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2015

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2.2 Dosing Information

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

5.1 Duration of Effect

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17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NARCAN Nasal Spray is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

NARCAN Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present.

NARCAN Nasal Spray is not a substitute for emergency medical care.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

NARCAN Nasal Spray is for intranasal use only.

No additional device assembly is required.

Because treatment of suspected opioid overdose must be performed by someone other than the patient, instruct the prescription recipient to inform those around them about the presence of NARCAN Nasal Spray and the *Instructions for Use*.

Instruct the patient or caregiver to read the *Instructions for Use* at the time they receive a prescription for NARCAN Nasal Spray. Emphasize the following instructions to the patient or caregiver:

- Administer NARCAN Nasal Spray as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death. Since the duration of action of most opioids exceeds that of naloxone hydrochloride and the suspected opioid overdose may occur outside of supervised medical settings, seek immediate emergency medical assistance, keep the patient under continued surveillance until emergency personnel arrive, and administer repeated doses of NARCAN Nasal Spray, as necessary. Always seek emergency medical assistance in the event of a suspected, potentially life-threatening opioid emergency after administration of the first dose of NARCAN Nasal Spray.
- Additional doses of NARCAN Nasal Spray may be required until emergency medical assistance becomes available.
- Do not attempt to reuse NARCAN Nasal Spray. Each NARCAN Nasal Spray contains a single dose of naloxone and cannot be reused.
- Re-administer NARCAN Nasal Spray, using a new nasal spray, every 2 to 3 minutes if the patient does not respond or responds and then relapses into respiratory depression.
- Administer NARCAN Nasal Spray in alternate nostrils with each dose.
- Administer NARCAN Nasal Spray according to the printed instructions on the device label and the *Instructions for Use*.

- Place the patient in the supine position. Prior to administration, be sure the device nozzle is inserted in either nostril of the patient, and provide support to the back of the neck to allow the head to tilt back. **Do not prime or test the device prior to administration.**
- To administer the dose press firmly on the device plunger.
- Remove the device nozzle from the nostril after use.
- Turn patient on their side as shown in the *Instructions for Use* and call for emergency medical assistance immediately after administration of the first dose of NARCAN Nasal Spray.

2.2 Dosing in Adults and Pediatric Patients

Initial Dosing

The recommended initial dose of NARCAN Nasal Spray in adults and pediatric patients is one spray delivered by intranasal administration, which delivers 4 mg of naloxone hydrochloride.

Repeat Dosing

Seek emergency medical assistance as soon as possible after administering the first dose of NARCAN Nasal Spray.

The requirement for repeat doses of NARCAN Nasal Spray depends upon the amount, type, and route of administration of the opioid being antagonized.

Administer NARCAN Nasal Spray in alternate nostrils with each dose.

If the patient responds to NARCAN Nasal Spray and relapses back into respiratory depression before emergency assistance arrives, administer an additional dose of NARCAN Nasal Spray using a new NARCAN Nasal Spray and continue surveillance of the patient.

If the desired response is not obtained after 2 or 3 minutes, administer an additional dose of NARCAN Nasal Spray using a new NARCAN Nasal Spray. If there is still no response and additional doses are available, administer additional doses of NARCAN Nasal Spray every 2 to 3 minutes using a new NARCAN Nasal Spray with each dose until emergency medical assistance arrives.

Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

2.3 Dosing Modifications due to Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and require higher doses of naloxone hydrochloride or repeated administration of NARCAN Nasal Spray using a new nasal spray [*see Warnings and Precautions (5.2)*].

3 DOSAGE FORMS AND STRENGTHS

NARCAN Nasal Spray is supplied as a single 4 mg dose of naloxone hydrochloride in a 0.1 mL intranasal spray.

4 CONTRAINDICATIONS

NARCAN Nasal Spray is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Recurrent Respiratory and Central Nervous System Depression

The duration of action of most opioids may exceed that of NARCAN Nasal Spray resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms. Therefore, it is necessary to seek emergency medical assistance immediately after administration of the first dose of NARCAN Nasal Spray and to keep the patient under continued surveillance. Administer additional doses of NARCAN Nasal Spray if the patient is not adequately responding or responds and then relapses back into respiratory depression, as necessary [*see Dosage and Administration (2.2)*]. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

5.2 Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses of naloxone hydrochloride may be required to antagonize buprenorphine because the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor [*see Dosage and Administration (2.3)*]. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

5.3 Precipitation of Severe Opioid Withdrawal

The use of NARCAN Nasal Spray in patients who are opioid-dependent may precipitate opioid withdrawal 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. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes. Monitor the patient for the development of the signs and symptoms of opioid withdrawal.

Abrupt postoperative reversal of opioid depression after using naloxone hydrochloride may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, after use of naloxone hydrochloride, monitor patients with

pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in an appropriate healthcare setting. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. In these settings, consider use of an alternative, naloxone-containing product that can be titrated to effect and, where applicable, dosed according to weight. [*see Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Precipitation of Severe Opioid Withdrawal [*see Warnings and Precautions (5.3)*]

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The following adverse reactions were observed in a NARCAN Nasal Spray clinical study.

In a pharmacokinetic study of 30 healthy adult volunteers exposed to one spray of NARCAN Nasal Spray in one nostril or two sprays of NARCAN Nasal Spray, one in each nostril, the most common adverse reactions were: increased blood pressure, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, and nasal inflammation.

The following adverse reactions have been identified primarily during post-approval use of naloxone hydrochloride in the post-operative setting. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia, and have caused agitation.

Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated an acute withdrawal syndrome. Signs and symptoms have included: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal signs and symptoms also included convulsions, excessive crying, and hyperactive reflexes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on naloxone use in pregnant women are not sufficient to inform a drug-associated risk. However, there are clinical considerations [see *Clinical Considerations*]. In animal reproduction studies, no embryotoxic or teratogenic effects were observed in mice and rats treated with naloxone hydrochloride during the period of organogenesis at doses equivalent to 6-times and 12-times, respectively, a human dose of 8 mg/day (two NARCAN Nasal Sprays) based on body surface area comparison [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Naloxone hydrochloride crosses the placenta, and may precipitate withdrawal in the fetus, as well as in the opioid-dependent mother [see *Warnings and Precautions (5.3)*]. The fetus should be evaluated for signs of distress after NARCAN Nasal Spray is used. Careful monitoring is needed until the fetus and mother are stabilized.

Data

Animal Data

Naloxone hydrochloride was administered during organogenesis to mice and rats at subcutaneous doses up to 10 mg/kg/day (equivalent to 6-times and 12-times, respectively, a human dose of 8 mg (two NARCAN Nasal Sprays)) (based on body surface area comparison). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.

Pregnant female rats were administered 2 or 10 mg/kg naloxone subcutaneously from Gestation Day 15 to Postnatal day 21. There were no adverse effects on the offspring (up to 12-times a human dose of 8 mg/day (two NARCAN Nasal Sprays) based on body surface area comparison).

8.2 Lactation

Risk Summary

There is no information regarding the presence of naloxone in human milk, or the effects of naloxone on the breastfed infant or on milk production. Studies in nursing mothers have shown that naloxone does not affect prolactin or oxytocin hormone levels. Naloxone is minimally orally bioavailable.

8.4 Pediatric Use

The safety and effectiveness of NARCAN Nasal Spray has been established in pediatric patients for known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Use of naloxone hydrochloride in pediatric patients is supported by evidence from adequate and well-controlled studies of naloxone hydrochloride in adults with additional

data from 15 clinical studies (controlled and uncontrolled) in which neonates and pediatric patients received parenteral naloxone hydrochloride in doses ranging from 0.005 mg/kg to 0.01 mg/kg. Safety and effectiveness are also supported by use of other naloxone hydrochloride products in the post-marketing setting, as well as data available in the medical literature and clinical practice guidelines. NARCAN Nasal Spray may be administered to pediatric patients of all ages.

Absorption of naloxone hydrochloride following intranasal administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds appropriately to naloxone hydrochloride, he/she must be carefully monitored for at least 24 hours, as a relapse may occur as naloxone hydrochloride is metabolized. In opioid-dependent pediatric patients, (including neonates), administration of naloxone hydrochloride may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening, if not recognized, and should be treated according to protocols developed by neonatology experts [*see Warnings and Precautions (5.3)*].

In settings such as in neonates with known or suspected exposure to maternal opioid use, where it may be preferable to avoid the abrupt precipitation of opioid withdrawal symptoms, consider use of an alternate naloxone-containing product that can be dosed according to weight and titrated to effect.

Also, in situations where the primary concern is for infants at risk for opioid overdose, consider whether the availability of alternate naloxone-containing products may be better suited than NARCAN Nasal Spray.

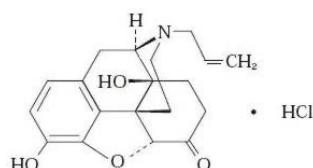
8.5 Geriatric Use

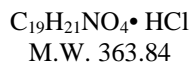
Geriatric patients have a greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Therefore, the systemic exposure of naloxone hydrochloride can be higher in these patients.

Clinical studies of naloxone hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11 DESCRIPTION

NARCAN (naloxone hydrochloride) Nasal Spray is a pre-filled, single dose intranasal spray. Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following structure:





Naloxone hydrochloride, an opioid antagonist, occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Each NARCAN Nasal Spray contains a single 4 mg dose of naloxone hydrochloride in a 0.1 mL intranasal spray.

Inactive ingredients include benzalkonium chloride (preservative), disodium ethylenediaminetetraacetate (stabilizer), sodium chloride, hydrochloric acid to adjust pH, and purified water. The pH range is 3.5 to 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation, and hypotension. It can also reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

In a pharmacokinetic study in 30 healthy adult subjects, the relative bioavailability (BA) of one nasal spray in one nostril (4 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution) and two nasal sprays administered as one nasal spray in each nostril (8 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution in each nostril) was compared to a single dose of 0.4 mg naloxone hydrochloride intramuscular injection. For intranasal administration, the subjects were instructed not to breathe through the nose during administration of the nasal spray, and remained fully supine for approximately one hour post-dose. For intramuscular administration, naloxone was administered as a single injection in the gluteus maximus muscle. The pharmacokinetic parameters obtained in the study are shown in Table 1.

Table 1 Mean Pharmacokinetic Parameters (CV%) for Naloxone Following NARCAN (Naloxone HCl) Nasal Spray and Intramuscular Injection of Naloxone HCl to Healthy Subjects

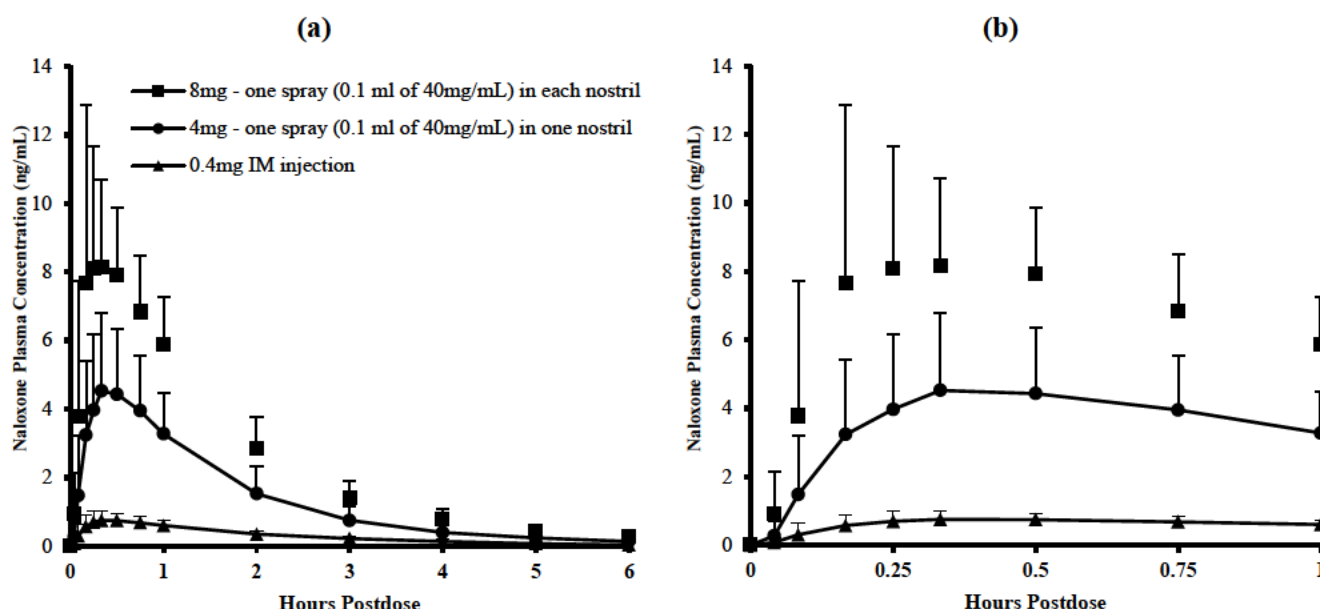
Parameter	4 mg – One Nasal Spray in one nostril	8 mg –Two Nasal Sprays, one in each nostril	0.4 mg Intramuscular Injection
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	(N=29)	(N=29)	(N=29)
t_{\max} (h) [†]	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
C_{\max} (ng/mL)	4.83 (43.1)	9.70 (36.0)	0.88 (30.5)
AUC _t (hr ng/mL)	7.87 (37.4)	15.3 (23.0)	1.72 (22.9)
AUC _{0-inf} (h*ng/mL)	7.95 (37.3)	15.5 (22.7)	1.76 (22.6)
$t_{1/2}$ (h)	2.08 (29.5)	2.10 (32.4)	1.24 (25.9)
Dose normalized Relative BA (%) vs. IM	46.7 (31.4) ^{††}	43.9 (23.8)	100

[†] t_{\max} reported as median (minimum, maximum)

^{††} N=28 for Relative BA.

Figure 1 Mean \pm SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intranasal Administration and Intramuscular Injection



The median naloxone t_{\max} after intranasal administration of NARCAN Nasal Spray (one nasal spray in one nostril or two nasal sprays as one spray in each nostril) was not significantly different compared to the 0.4 mg dose of naloxone hydrochloride intramuscular injection (Table 1).

The dose normalized relative bioavailability of one (4 mg) or two doses (8 mg) of NARCAN Nasal Spray as compared to the 0.4 mg dose of naloxone hydrochloride administered by intramuscular injection was 46.7%, and 43.9%, respectively.

Distribution

Following parenteral administration, naloxone is distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent, but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

Elimination

Following a single intranasal administration of NARCAN Nasal Spray (4 mg dose of naloxone hydrochloride), the mean plasma half-life of naloxone in healthy adults was approximately 2.08 (30% CV) hours, which was longer than that observed after administrations of a 0.4 mg naloxone hydrochloride intramuscular injection, where the half-life was 1.24 hours (26% CV). In a neonatal study of naloxone hydrochloride injection, the mean (\pm SD) plasma half-life was observed to be 3.1 (\pm 0.5) hours.

Metabolism

Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation, with naloxone-3-glucuronide as the major metabolite.

Excretion

After an oral or intravenous dose, about 25-40% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.

Impairment of Fertility

Male rats were treated with 2 or 10 mg/kg naloxone for 60 days prior to mating. Female rats treated for 14-days prior to mating and throughout gestation with the same doses of naloxone (up to 12-times a human dose of 8 mg/day (two NARCAN Nasal Sprays) based on body surface area comparison). There was no adverse effect on fertility.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Carton containing two blister packages each with a single NARCAN Nasal Spray (single 4 mg dose of naloxone hydrochloride intranasal spray).

NARCAN Nasal Spray is not made with natural rubber latex.

16.2 Storage and Handling

Store NARCAN Nasal Spray in the blister and cartons provided.

Store at controlled room temperature 59°F to 77°F (15°C to 25°C). Excursions permitted between 4°C to 40°C (39°F to 104°F). Do not freeze. Protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient and family members or caregivers to read the FDA-approved patient labeling (*Patient Information* and *Instructions for Use*).

Recognition of Opioid Overdose

Inform patients and their family members or caregivers about how to recognize the signs and symptoms of an opioid overdose such as the following:

- Extreme somnolence - inability to awaken a patient verbally or upon a firm sternal rub.
- Respiratory depression - this can range from slow or shallow respiration to no respiration in a patient who is unarousable.
- Other signs and symptoms that may accompany somnolence and respiratory depression include the following:
 - Miosis.
 - Bradycardia and/or hypotension.

Risk of Recurrent Respiratory and Central Nervous System Depression

Instruct patients and their family members or caregivers that, since the duration of action of most opioids may exceed that of NARCAN Nasal Spray, they must seek immediate emergency medical assistance after the first dose of NARCAN Nasal Spray and keep the patient under continued surveillance [*see Dosage and Administration (2.2), Warnings and Precautions (5.3)*].

Limited Efficacy for/with Partial Agonists or Mixed Agonist/Antagonists

Instruct patients and their family members or caregivers that the reversal of respiratory depression caused by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and may require higher doses of naloxone hydrochloride or repeated administration of NARCAN Nasal Spray, using a new nasal spray each time [*see Dosage and Administration (2.3), Warnings and Precautions (5.2)*].

Precipitation of Severe Opioid Withdrawal

Instruct patients and their family members or caregivers that the use of NARCAN Nasal Spray in patients who are opioid dependent may precipitate opioid withdrawal [*see Warnings and Precautions (5.3), Adverse Reactions (6)*].

Administration Instructions

Instruct patients and their family members or caregivers to:

- Ensure NARCAN Nasal Spray is present whenever persons may be intentionally or accidentally exposed to an opioid overdose (i.e., opioid emergencies).
- Administer NARCAN Nasal Spray as quickly as possible if a patient is unresponsive and an opioid overdose is suspected, even when in doubt, because prolonged respiratory depression may result in damage to the central nervous system or death. **NARCAN Nasal Spray is not a substitute for emergency medical care** [see *Dosage and Administration (2.1)*].
- Lay the patient on their back and administer NARCAN Nasal Spray into one nostril while providing support to the back of the neck to allow the head to tilt back [see *Dosage and Administration (2.1)*].
- Use each nasal spray only one time [see *Dosage and Administration (2.1)*].
- Turn patient on their side as shown in the *Instructions for Use* and call for emergency medical assistance immediately after administration of the first dose of NARCAN Nasal Spray. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance [see *Dosage and Administration (2.1)*].
- Monitor patients and re-administer NARCAN Nasal Spray using a new NARCAN Nasal Spray every 2 to 3 minutes, if the patient is not responding or responds and then relapses back into respiratory depression. Administer NARCAN Nasal Spray in alternate nostrils with each dose [see *Dosage and Administration (2.1)*].
- Replace NARCAN Nasal Spray before its expiration date.

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PATIENT INFORMATION
NARCAN (nar´ kan)
(naloxone hydrochloride)
Nasal Spray

You and your family members or caregivers should read this Patient Information leaflet before an opioid emergency happens. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about NARCAN Nasal Spray?

NARCAN Nasal Spray is used to temporarily reverse the effects of opioid medicines. The medicine in NARCAN Nasal Spray has no effect in people who are not taking opioid medicines. Always carry NARCAN Nasal Spray with you in case of an opioid emergency.

1. Use NARCAN Nasal Spray right away if you or your caregiver think signs or symptoms of an opioid emergency are present, even if you are not sure, because an opioid emergency can cause severe injury or death. Signs and symptoms of an opioid emergency may include:
 - unusual sleepiness and you are not able to awaken the person with a loud voice or by rubbing firmly on the middle of their chest (sternum)
 - breathing problems including slow or shallow breathing in someone difficult to awaken or who looks like they are not breathing
 - the black circle in the center of the colored part of the eye (pupil) is very small, sometimes called “pinpoint pupils,” in someone difficult to awaken
2. Family members, caregivers, or other people who may have to use NARCAN Nasal Spray in an opioid emergency should know where NARCAN Nasal Spray is stored and how to give NARCAN before an opioid emergency happens.
3. **Get emergency medical help right away after giving the first dose of NARCAN Nasal Spray.** Rescue breathing or CPR (cardiopulmonary resuscitation) may be given while waiting for emergency medical help.
4. The signs and symptoms of an opioid emergency can return after NARCAN Nasal Spray is given. If this happens, give another dose after 2 to 3 minutes using a new NARCAN Nasal Spray and watch the person closely until emergency help is received.

What is NARCAN Nasal Spray?

- NARCAN Nasal Spray is a prescription medicine used for the treatment of an opioid emergency such as an overdose or a possible opioid overdose with signs of breathing problems and severe sleepiness or not being able to respond.
- NARCAN Nasal Spray is to be given right away and does not take the place of emergency medical care. Get emergency medical help right away after giving the first dose of NARCAN Nasal Spray, even if the person wakes up.
- NARCAN Nasal Spray is safe and effective in children for known or suspected opioid overdose.

Who should not use NARCAN Nasal Spray?

Do not use NARCAN Nasal Spray if you are allergic to naloxone hydrochloride or any of the ingredients in NARCAN Nasal Spray. See the end of this leaflet for a complete list of ingredients in NARCAN Nasal Spray.

What should I tell my healthcare provider before using NARCAN Nasal Spray?

Before using NARCAN Nasal Spray, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems
- are pregnant or plan to become pregnant. Use of NARCAN Nasal Spray may cause withdrawal symptoms in your unborn baby. Your unborn baby should be examined by a healthcare provider right away after you use NARCAN Nasal Spray.
- are breastfeeding or plan to breastfeed. It is not known if NARCAN Nasal Spray passes into your breast milk.

Tell your healthcare provider about the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use NARCAN Nasal Spray?

Read the “Instructions for Use” at the end of this Patient Information leaflet for detailed information about the right way to use NARCAN Nasal Spray.

- Use NARCAN Nasal Spray exactly as prescribed by your healthcare provider.
- Each NARCAN Nasal Spray contains only 1 dose of medicine and cannot be reused.
- Lay the person on their back. Support their neck with your hand and allow the head to tilt back before giving NARCAN Nasal Spray.
- NARCAN Nasal Spray should be given into one nostril.
- If additional doses are needed, give NARCAN Nasal Spray in the other nostril.

What are the possible side effects of NARCAN Nasal Spray?

NARCAN Nasal Spray may cause serious side effects, including:

- **Sudden opioid withdrawal symptoms.** In someone who has been using opioids regularly, opioid withdrawal symptoms can happen suddenly after receiving NARCAN Nasal Spray and may include:
 - body aches
 - diarrhea
 - increased heart rate
 - fever
 - runny nose
 - sneezing
 - goose bumps
 - sweating
 - yawning
 - nausea or vomiting
 - nervousness
 - restlessness or irritability
 - shivering or trembling
 - stomach cramping
 - weakness
 - increased blood pressure

In infants under 4 weeks old who have been receiving opioids regularly, sudden opioid withdrawal may be life-threatening if not treated the right way. Signs and symptoms include: seizures, crying more than usual, and increased reflexes.

These are not all of the possible side effects of NARCAN Nasal Spray. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NARCAN Nasal Spray?

- Store NARCAN Nasal Spray at room temperature between 59°F to 77°F (15°C to 25°C). NARCAN Nasal Spray may be stored for short periods between 39°F to 104°F (4°C to 40°C).
- Do not freeze NARCAN Nasal Spray.
- Keep NARCAN Nasal Spray in its box until ready to use. Protect from light.
- Replace NARCAN Nasal Spray before the expiration date on the box.

Keep NARCAN Nasal Spray and all medicines out of the reach of children.

General information about the safe and effective use of NARCAN Nasal Spray.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NARCAN Nasal Spray for a condition for which it was not prescribed. You can ask your pharmacist or healthcare provider for information about NARCAN Nasal Spray that is written for health professionals.

What are the ingredients in NARCAN Nasal Spray?

Active ingredient: naloxone hydrochloride

Inactive ingredients: benzalkonium chloride (preservative), disodium ethylenediametetraacetate (stabilizer), sodium chloride, hydrochloric acid to adjust pH and sterile water

NARCAN Nasal Spray is not made with natural rubber latex.

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For more information, go to www.narcannasalspray.com or call 1-844-4NARCAN (1-844-462-7226).

This Patient Information has been approved by the U.S. Food and Drug Administration.

Issued: 11/2015

Instructions for Use NARCAN (nar' kan) (naloxone hydrochloride) Nasal Spray

You and your family members or caregivers should read the Instructions for Use that comes with NARCAN Nasal Spray before using it. Talk to your healthcare provider if you and your family members or caregivers have any questions about the use of NARCAN Nasal Spray.

Use NARCAN Nasal Spray for known or suspected opioid overdose in adults and children.

Important: For use in the nose only.

- **Do not remove or test the NARCAN Nasal Spray until ready to use.**
- **Each NARCAN Nasal Spray has 1 dose and cannot be reused.**
- **You do not need to prime NARCAN Nasal Spray.**

How to use NARCAN nasal spray:

Step 1. Lay the person on their back to receive a dose of NARCAN Nasal Spray.

Step 2. Remove NARCAN Nasal Spray from the box. Peel back the tab with the circle to open the NARCAN Nasal Spray.



Step 3. Hold the NARCAN Nasal Spray with your thumb on the bottom of the plunger and your first and middle fingers on either side of the nozzle.



Step 4. Tilt the person's head back and provide support under the neck with your hand. Gently insert the tip of the nozzle into **one nostril** until your fingers on either side of the nozzle are against the bottom of the person's nose.



Step 5. Press the plunger firmly to give the dose of NARCAN Nasal Spray.



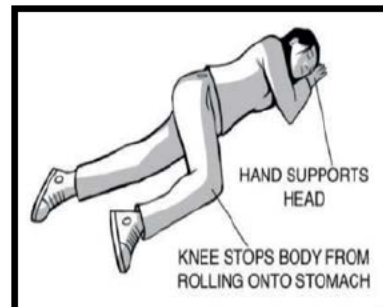
Step 6. Remove the NARCAN Nasal Spray from the

nostril after giving the dose.

What to do after NARCAN Nasal Spray has been used:

Step 7. Get emergency medical help right away.

- Move the person on their side (recovery position) after giving NARCAN Nasal Spray.
- Watch the person closely.
- If the person does not respond by waking up, to voice or touch, or breathing normally another dose may be given. NARCAN Nasal Spray may be dosed every 2 to 3 minutes, if available.
- Repeat **Steps 2 through 6** using a new NARCAN Nasal Spray to give another dose in the other nostril. If additional NARCAN Nasal Sprays are available, Steps 2 through 6 may be repeated every 2 to 3 minutes until the person responds or emergency medical help is received.



Step 8. Put the used NARCAN Nasal Spray back into its box.

Step 9. Throw away (dispose of) the used NARCAN Nasal Spray in a place that is away from children.

How should I store NARCAN Nasal Spray?

- Store NARCAN Nasal Spray at room temperature between 59°F to 77°F (15°C to 25°C). NARCAN Nasal Spray may be stored for short periods between 39°F to 104°F (4°C to 40°C).
- Do not freeze NARCAN Nasal Spray.
- Keep NARCAN Nasal Spray in the box until ready to use. Protect from light.
- Replace NARCAN Nasal Spray before the expiration date on the box.

Keep NARCAN Nasal Spray and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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For more information, go to www.narcannasalspray.com or call 1-844-4NARCAN (1-844-462-7226).

Issued: 11/2015

NARCAN[®] (naloxone HCl) **NASAL SPRAY**

QUICK START GUIDE Opioid Overdose Response Instructions

Use NARCAN Nasal Spray (naloxone hydrochloride) for known or suspected opioid overdose in adults and children.

Important: For use in the nose only.

Do not remove or test the NARCAN Nasal Spray until ready to use.

1 Identify Opioid Overdose and Check for Response

Ask person if he or she is okay and shout name.

Shake shoulders and firmly rub the middle of their chest.

Check for signs of opioid overdose:

- Will not wake up or respond to your voice or touch
- Breathing is very slow, irregular, or has stopped
- Center part of their eye is very small, sometimes called “pinpoint pupils”

Lay the person on their back to receive a dose of NARCAN Nasal Spray.



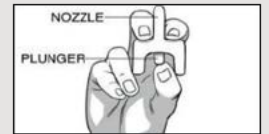
2 Give NARCAN Nasal Spray

Remove NARCAN Nasal Spray from the box.

Peel back the tab with the circle to open the NARCAN.



Hold the NARCAN nasal spray with your thumb on the bottom of the plunger and your first and middle fingers on either side of the nozzle.



Gently insert the tip of the nozzle into either nostril.

- Tilt the person's head back and provide support under the neck with your hand. Gently insert the tip of the nozzle into **one nostril**, until your fingers on either side of the nozzle are against the bottom of the person's nose.



Press the plunger firmly to give the dose of NARCAN Nasal Spray.

- Remove the NARCAN Nasal Spray from the nostril after giving the dose.



3 Call for emergency medical help, Evaluate, and Support

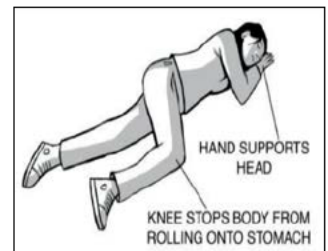
Get emergency medical help right away.

Move the person on their side (recovery position)

after giving NARCAN Nasal Spray.

Watch the person closely.

If the person does not respond by waking up, to voice or touch, or breathing normally another dose may be given. NARCAN Nasal Spray may be dosed every 2 to 3 minutes, if available.



Repeat Step 2 using a new NARCAN Nasal Spray to give another dose in the other nostril. If additional NARCAN Nasal Sprays are available, repeat step 2 every 2 to 3 minutes until the person responds or emergency medical help is received.

For more information about NARCAN Nasal Spray, go to www.narcannasalspray.com, or call 1-844-4NARCAN (1-844-462-7226) 159 of 236

Role of Naloxone in Opioid Overdose Fatality Prevention

Post Meeting Summary

Naloxone is an opioid receptor antagonist that is approved for use by injection only for the reversal of opioid overdose and for adjunct use in the treatment of septic shock. It is currently being used mainly in emergency departments and in ambulances by trained medical professionals. There have been efforts to expand its use by providing the drug to some patients with take-home opioid prescriptions and those who inject illicit drugs, potentially facilitating earlier administration of the drug. On April 12, 2012, FDA, CDC, NIDA and the HHS Office of the Assistant Secretary for Health sponsored a public meeting to initiate a discussion about whether naloxone should be made more widely available outside of conventional medical settings. A link to the meeting page that contains additional information is located here:

<http://www.fda.gov/Drugs/NewsEvents/ucm277119.htm>.

Meeting Highlights

- The White House Office of National Drug Control Policy (ONDCP) Prescription Drug Abuse Prevention Plan includes a discussion of naloxone. A statement on behalf of ONDCP Director, Gil Kerlikowske, was read at the meeting. It noted that the Obama Administration recognizes “the important role naloxone can play in overcoming drug overdoses,” as articulated in its 2010 National Drug Control Strategic Plan.
- In the United States, mortality rates closely correlate with opioid sales. In 2008, approximately 36,450 people died from drug overdoses. At least 14,800 of these deaths involved prescription opioid analgesics. Moreover, according to the Substance Abuse and Mental Health Services Administration, the number/rate of Americans 12 years of age and older who currently abuse pain relievers has increased by 20 percent between 2002 and 2009.
- The UN Commission on Narcotics Drugs “encourages all Member States to include effective elements for the prevention and treatment of drug overdose, in particular opioid overdose, in national drug policies, where appropriate, and to share best practices and information on the prevention and treatment of drug overdose, in particular opioid overdose, including the use of opioid receptor antagonists such as naloxone.”
- Most speakers agreed that there should be easier access to naloxone. One speaker said that better data are needed on whether naloxone is effective in saving lives. One issue to be addressed is the relatively short half-life of naloxone compared to some longer-acting opioid formulations. After naloxone is administered, it is important to seek immediate medical attention.

- Speakers commented on the concern that increasing the overall availability of naloxone might lead to increased drug use by giving a false sense of security, and suggested this was not a likely concern. An overview of research related to attitudes and behaviors related to STDs, and in particular to HPV vaccination (Gardasil), presented at the meeting reported no association with an increase in unprotected sex among sexually active women. Similarly, no evidence for greater risk-taking has been seen in the area of protective equipment to prevent childhood injuries (such as bike helmets). One speaker said that such interventions do not necessarily lead to more risky behaviors. Instead, the results are dependent on the prevention strategy, the target of the strategy, individual characteristics and the larger social context.
- Most speakers participating in the open public hearing, some of whom had lost family members or friends to opioid overdose, recommended that the use of naloxone be switched to over-the-counter (OTC) status and encouraged FDA to quickly take steps to improve access to the drug, including by approving non-injectable forms (e.g., intranasal) of the drug.
- FDA discussed the general pathways to expand access to naloxone through the development of new formulations or making naloxone approved for use over the counter (OTC).
 - Gaining FDA approval for a new naloxone formulation, such as an intranasal or auto-injector form, would require a bioequivalence study. In such a trial, drug levels with the new and injectable forms of naloxone would be compared. Such studies typically require fewer than 100 subjects. Data related to safety, chemistry and manufacturing as well as data related to the device used to administer the drug are necessary.
 - Switching naloxone to over the counter would likely require additional clinical data that answers the following questions:
 - Can patients (or their caregivers) understand the directions?
 - Can patients (or their caregivers) follow the directions?
 - Can patients (or their caregivers) properly decide if they should use the product?

In addition, data would need to be collected on the new naloxone product to see if OTC consumers are able to use it safely.

Speakers agreed that there is a need for better coordination among Federal agencies, manufacturers and other stakeholder groups to resolve regulatory issues and improve access to the drug. The meeting ended with each of the Federal partners expressing a willingness to work with interested manufacturers and developers to further explore the best uses of naloxone to prevent opioid overdose deaths.

**Exploring Naloxone Uptake and Use
Public Meeting
July 1 and 2, 2015

Summary Report**

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Exploring Naloxone Uptake and Use

July 1 and 2, 2015, Public Meeting

Meeting Summary

The Problem

The United States is experiencing an opioid overdose epidemic. In 2013, more than 16,000 people died from a prescription opioid overdose—about one death every 33 minutes.¹ Overall, overdose deaths in the United States now outnumber deaths from motor vehicle crashes.² The increase in opioid prescriptions during the last decade has contributed to this epidemic. Whereas in the 1990s opioids were used primarily to treat end-of-life and acute cancer pain, they are now also being prescribed to treat non-cancer pain associated with osteoarthritis, rheumatoid arthritis, lower back problems, fibromyalgia, and dental surgery. Unfortunately, treatment capacity remains limited. A March 2015 *American Journal of Public Health* article titled [National and State Treatment Need and Capacity for Opioid Agonist Medication-Assisted Treatment](#) concluded that there are “significant gaps between treatment need and capacity . . . at the state and national levels.”

As summarized in this report, numerous efforts are underway to reduce the risk of death from opioid overdose. Local community-based organizations have taken the lead in this effort. They have helped reduce overdose deaths among their clients, mostly illicit drug users, by making the prescription drug naloxone available, often at low or no cost, to their clients and clients’ friends and family members. During the past several years, state and federal public health organizations have launched a variety of programs around the country with the goal of stemming the overdose epidemic. Nevertheless, presenters and participants at this meeting expressed concern that many of the efforts underway to reduce opioid overdose are not reaching the U.S. population in general; that certain populations remain at high risk; and that the broad U.S. population needs more information about the risk of opioid overdose, the causes and signs of addiction and overdose, available drug treatment options, and the availability of naloxone to reverse overdose.

The Centers for Disease Control and Prevention (CDC) describes persons at increased risk for prescription opioid overdose as disproportionately male, non-Hispanic white, poor and rural, people who increase their opioid dose (as dose increases, risk of overdose increases), and people who doctor- and pharmacy-shop, hoping to obtain additional pills.³

Naloxone

Naloxone is an opioid receptor antagonist that can rapidly reverse the overdose of either prescription (e.g., OxyContin) or illicit (e.g., heroin) opioids. Historically, naloxone has been most commonly used by trained medical personnel in hospital emergency departments and on ambulances. However, with the rise in prescription opioid use and the associated rise in overdose deaths, naloxone, preceded or followed by a 911 call, has assumed a larger role in the outpatient setting and is increasingly being used by non-medical personnel to reverse overdose.

¹ Grant Baldwin, Director, Division of Unintentional Injury Prevention, Centers for Disease Control and Prevention (CDC).

² Michael Botticelli, Director, National Drug Control Policy, Executive Office of the President.

³ Grant Baldwin, CDC.

The only naloxone therapy with an indication for bystander use is an injectable medicine—Evzio, a take-home auto-injector approved by the Food and Drug Administration (FDA) in April 2014. Although intranasal versions of naloxone are also available, they are not FDA-approved and so their safety and efficacy compared to injectable versions are not known—the intranasal versions are created from the generic injectable naloxone and packaged and distributed in kit form. Applications for two intranasal formulations have been submitted to FDA for marketing approval and are undergoing FDA expedited review.

The Public Meeting

On July 1 and 2, 2015, representatives from academia, government, community-based organizations, industry, and patient advocacy groups came together at FDA’s White Oak campus in Silver Spring, Maryland, to discuss a variety of scientific, legal, regulatory, logistical, and clinical issues surrounding the use of naloxone. This was the second federal public meeting on this topic; the first was a one-day workshop at FDA on [April 12, 2012](#)⁴ to discuss the value of wider availability of naloxone, beyond the more common medical settings, to reduce the incidence of opioid overdose deaths and to hear from the public on related issues of concern.

The overarching topics discussed at the 2015 public meeting, titled ***Exploring Naloxone Uptake and Use***, included identifying which populations are most at risk for opioid overdose, what progress has been made since the 2012 meeting in expanding the availability of naloxone, and what public health organizations around the country can do to keep up the momentum achieved since 2012 to ensure the growth and sustainability of existing programs while expanding naloxone availability to new populations.

The 2015 meeting was organized through a collaboration of FDA, the National Institute of Drug Abuse (NIDA), the CDC, the Substance Abuse and Mental Health Services Administration (SAMHSA), and the Health Resources and Services Administration (HRSA). Detailed information about the meeting, including most slide presentations, a web cast, the full transcript, and this summary report, are available on FDA’s [2015 Naloxone Meeting](#) web page.⁵ The following summary highlights key themes and findings, organized primarily around the meeting agenda.

Meeting Summary

Peter Lurie, Associate Commissioner, Office of Public Health Strategy and Analysis (FDA), welcomed attendees, noting how much progress had been made since the first meeting in 2012 and crediting those accomplishments to “the hard work and dedication of people in this very room, people who pioneered these programs, who were willing to advocate for them, to actually carry them out. . . .”

Michael Botticelli, Director of the Office of National Drug Control Policy (ONDCP), Executive Office of the President, and Grant Baldwin, Director, Division of Unintentional Injury Prevention at CDC, provided introductory remarks. They set the stage by describing the extent of non-medical use of opioids in the

⁴ See more about the 2012 workshop on FDA’s web page at <http://www.fda.gov/Drugs/NewsEvents/ucm277119.htm>. Accessed, September 2015.

⁵ See FDA’s web page at <http://www.fda.gov/drugs/newsevents/ucm442236.htm> for more information on the 2015 meeting. Accessed, September 2015.

United States today, including the use of prescription opioids, and the dramatic increase in opioid-related deaths during the past decade.

Michael Botticelli noted that although the numbers of overdoses from prescription opioid use dropped slightly in 2013, the reduction was offset by an increase in heroin use and deaths—some individuals move from prescription opioids to heroin when opioids are no longer easy to obtain. He expressed his concern that so many people are still unaware of the existence of naloxone—what it does and how to obtain it—emphasizing that although much has been achieved since the 2012 meeting, more work is needed. He emphasized that his office, ONDCP, will continue to support the many efforts of the people present at this meeting. The U.S. [National Drug Control Strategy](#) has noted the importance of naloxone since 2012.⁶

Grant Baldwin provided the context of the meeting, giving attendees an in-depth review of the latest statistics on the public health burden of prescription drug- and heroin-related overdoses (see his slide presentation for details on use, geographic locations of highest use, overdose, and overdose fatalities, among other details).

I. *Naloxone Use Today—Recent Trends*

Naloxone use among illicit drug users, first responders, and family members is growing as a direct result of an increase in the number of programs that address opioid education, overdose, and treatment at national, state, and local levels. The [World Health Organization](#) has issued guidelines on community management of opioid overdose.⁷ Local and national policies for the use of naloxone have expanded in the United Kingdom (U.K.). State and local programs in the United States have expanded recently as well. With this increase in use have also come changes in the market structure and pricing trends for naloxone.

- Naloxone is increasingly available in the United States, in different formulations.
 - According to the IMS data, sales of the 0.4 milligram per milliliter strength (primarily used in vials) make up about 70 to 80 percent of the total sold in a given year; sales of the one milligram per milliliter strength (reported to be used intranasally as well as by injection) make up the rest. These formulations have had sales on the order of hundreds of thousands to millions per year since April 2014 (launch of Evzio).
 - For Evzio, wholesaler distribution has increased since its launch, rising from less than 1,000 per quarter initially to more than 2,500 per quarter at the beginning of 2015. Evzio sales remain well below the sales of other formulations.
- The share of outpatient use of naloxone has risen sharply since 2009.
 - Sales of naloxone from wholesalers to outpatient settings increased by 72 percent during the last 5 years while sales to inpatient or emergency room settings declined by 12 percent.
- The number of sites/persons dispensing naloxone has increased.

⁶ The *National Drug Control Strategy* is available at https://www.whitehouse.gov/sites/default/files/ondcp/2012_ndcs.pdf. Accessed, October 2015.

⁷ See World Health Organization at http://www.who.int/substance_abuse/publications/management_opioid_overdose/en/. Accessed, October 2015.

- A June 2015 CDC [Morbidity and Mortality Weekly Report](#) showed a 243% increase in the number of sites that provide naloxone, a 183% increase in the number of laypersons providing naloxone kits, and a 160% increase in the number of overdose reversals. Of 26,000 reversals since the mid-1990s, 8,000 took place in 2013.⁸
- The Chicago Recovery Alliance was the first organization to distribute naloxone in the U.S. and has been doing so for 18 years. To date, they have distributed naloxone to over 38,000 people and received more than 6,000 reports of peer-reversals with naloxone.
- New York has a sizable program, including an initiative called Learning to Cope. This initiative makes naloxone and training available to prisoners⁹ and their families just before their release from prison.
 - Prisoners with a history of drug use are at greatest mortality risk during the first couple of weeks after release from prison. This is the population targeted in the study.
 - Prisoners due for release were identified and given “standard care” or standard care plus naloxone kits.
 - Although the final results have not been tabulated, the findings so far from interviews are that “two to three uses of naloxone [are happening] on another person for each time it’s used on the individual to whom we’ve assigned it.”
 - No evidence was found that providing naloxone was associated with a safety risk.
- A number of states have very active community drug addiction/public health organizations that are making naloxone and treatment options available to drug users and their families, individuals on opioid pain therapy and their families, and others who may come in contact with individuals at risk of overdose. Presenters described efforts under way in North Carolina, New York, Massachusetts, Ohio, and Rhode Island.
- Many presenters advocated wider naloxone availability.
 - Community-based advocacy groups have been the leaders in making naloxone available among certain populations (e.g., illicit drug users who can obtain it, for example, from needle exchange programs).
 - For many reasons (historical, political, legal, financial, organizational), naloxone has been and remains much less available to individuals at increased risk who are not considered part of the drug user category (e.g., individuals on opioids for long-term for pain or their families; individuals and their families who are in treatment for addiction disorder; individuals leaving prison; and individuals in rural communities with limited access to public health facilities). At the time of the meeting, only 19 states included the FDA-approved auto injector Evzio on their Medicaid formulary.
- There was a call from several presenters and speakers in the Open Public Hearing for a broad public health intervention to reach these additional populations more comprehensively.

⁸ See the report at <http://stacks.cdc.gov/view/cdc/31626#relatedDocuments>. Accessed, October 2015.

⁹ Prisoners are also the focus of a study underway in England. See the presentation by John Strang (day-one transcript, beginning on page 77) for a detailed analysis of the prisoner release study, the N-ALIVE prison release trial.

II. Identifying Patients in Need and Getting Naloxone to Them—National Programs

A number of national efforts have been successful in identifying patients at risk of overdose. In two examples, since 2012, SAMSHA and the U.S. Department of Veterans Affairs (VA) have launched large programs to help identify individuals who should have access to naloxone. Both programs make a range of information available to the public and support co-prescribing (see Section IV).

- SAMSHA has an [Opioid Overdose Toolkit](#), available online,¹⁰ that provides a variety of information about prescribing naloxone and other issues of interest to communities, families, first responders, and those in treatment. The toolkit also can help prescribers minimize the risk of opioid overdose through adherence to clinical practices. The number of people accessing the toolkit has increased significantly in recent years. Since the launch of the toolkit in August 2013, there have been 56,430 downloads of the entire toolkit or sections of it. It will be updated in the near future, so suggestions for input were invited. SAMSHA is also exploring the identification of optimal distribution points for naloxone in rural or resource-poor areas or to reach other specific populations at risk.
- The VA has an extensive program, launched two years ago, that includes prescribing naloxone and providing overdose education. The VA experience is an example of how to quickly move from community-based best practices to a large medical system framework.
 - The VA effort was built on the experience and knowledge of other organizations, including community-based groups around the country, on what was learned at the workshop on opioid overdose in 2012, and on information gathered from discussions with colleagues with similar experience in Scotland.
 - The program is based on prevention education. The VA provides a kit containing prevention and safety information, information on the use of the naloxone, two doses of naloxone, a face shield for rescue breathing, and disposable gloves. Prescribers receive example prescription forms to use with their patients and information on how to identify a patient who is a likely candidate for receiving a kit. Videos on the program are available on YouTube.
 - As of July 1, 2015, the VA had 79 reported opioid overdose reversals with over 5,400 kits dispensed. In many cases, the kits are being used to reverse overdoses in individuals other than those who originally received the kit.

III. Clinical, Legal, and Other Barriers

According to presenters and comments made during the public sessions, a number of barriers remain to making naloxone more widely available.

Prescription Status

- Some asserted that naloxone's prescription status is a barrier that prevents the medication from reaching locations where it may be needed most, such as public parks, bars, and specific neighborhoods.

¹⁰ Information about the Toolkit is available at <http://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit-Updated-2014/SMA14-4742>. Accessed, October 2015.

- Many people at highest risk (nonprescription opioid and other illicit drug users) don't necessarily access the traditional medical system.
- Within the traditional medical system, many patients and prescribers are unaware of or uncertain about naloxone. Physician acceptance of naloxone use could be a focus of future interventions.
 - Patients at risk who see medical professionals may feel uncomfortable asking for naloxone even when they know about it, because that might identify them as drug users.
 - Doctors may not know about it or may feel uncomfortable offering it.
 - In a North Carolina health professional education program, prescribers identified not knowing how to discuss the topic with their patients and not wanting to offend patients as obstacles to naloxone provision; some prescribers insisted that opioid misuse is not an issue in their practice (Project Lazarus).
 - One public commenter suggested making education about overdose and naloxone use a mandatory component of becoming an addiction-certified physician. Establishing a program for distribution of naloxone to people at risk could become a requirement for accreditation by the Joint Commission or the Commission on Accreditation of Rehabilitation Facilities (CARF).¹¹

Legal issues

- The legal situation with regard to reporting overdoses and prescribing naloxone remains in flux. All states have a civil Good Samaritan law, providing some civil immunity to people who stop at an emergency situation and render aid in good faith. However, overdose witnesses are typically concerned about possible criminal action, not civil liability. Fear of arrest and/or prosecution for drug use can prevent overdose witnesses from calling for emergency help.
- As of July 2015, 33 states had passed laws providing limited criminal liability to people who call 911 to report an overdose. These laws vary from state to state in terms of whom they cover and the extent of coverage.
 - Many of the laws provide immunity from prosecution, but not arrest, to those summoning emergency assistance in the case of an overdose.
 - Most of the laws only provide protection from minor drug law violations, but some extend the protection to other crimes.
 - In general, more recently passed laws provide more protection, with some newer laws providing protection from arrest as well as probation and parole violations, in addition to protection from prosecution.
- The majority of states have also taken steps to remove legal and regulatory barriers to naloxone access and remove any possible liability for prescribing, dispensing, or administering naloxone in good faith.
 - At the time of the meeting, 39 states had enacted naloxone access laws, which provide civil or criminal immunity for naloxone administration by licensed health care providers or lay responders.

¹¹ CARF is an international, independent, nonprofit accreditor of health and human services organizations.

- The majority of states permit naloxone to be prescribed to people other than a prescriber's patients, and most states permit it to be prescribed via standing or protocol order. Approximately a dozen states explicitly permit naloxone to be dispensed by laypeople, in addition to traditional pharmacies.
- Increasing costs are a barrier.
 - In the late 1990s, a 10cc vial of naloxone cost \$1.43 and a 1cc vial, as little as 20 cents.
 - Recent price increases (in January 2014) for the 0.4 milligram per milliliter strength and (in September 2014) for the one milligram per milliliter strength were 50 and 60 percent, respectively.
 - In 2014, 25 percent of all generic injectable molecules had at least one formulation with a month-to-month price increase of 60 percent or more.
- The price of naloxone has strained public health budgets as well as those of community-based harm reduction organizations.

IV. *Naloxone Co-prescribing*

Co-prescribing naloxone alongside the opioids provided in community-based office settings was recommended by many presenters and commenters during the open segment of the meeting.

- There was agreement that co-prescribing involves more than writing a prescription. Ideally, it entails provider education, substance-use assessments, overdose prevention toolkits, patient and family education, and referral to treatment programs, among other elements.
 - A number of community programs (e.g., Project Lazarus in North Carolina) have been working to educate prescribers, some of whom have not supported co-prescribing programs because they think they might be enabling patients.
 - The risk of prescription opioid abuse can be minimized by using appropriate patient screening, rational prescribing, and abuse-deterrent formulations. With a good script on how to talk to patients and to families, co-prescribing can be made much more understandable.
 - Offering to co-prescribe can be the beginning of a conversation to address the critical elements of a potential drug problem (e.g., risks of using opioids, risk of overdose, naloxone use, and treatment options) and can even be useful in identifying patients who wish to end long-term opioid use.
- Awareness of naloxone availability and comfort with prescribing the drug appear to be key hurdles for prescribers. One suggestion was to create a Drug Enforcement Administration (DEA) program that ensures that all prescribers who obtain DEA numbers are made aware of the availability of naloxone and their ability to co-prescribe it.
- Clinicians can use Prescription Drug Monitoring Programs (PDMPs), available in all but one state, to help guide their opioid/naloxone prescribing decisions. PDMPs collect, monitor, and analyze electronically transmitted prescribing and dispensing data submitted by pharmacies and dispensing practitioners. The data are used to support state efforts in education, research, enforcement, and abuse prevention. Physicians can look up patient opioid use, including prescribing by other practitioners, before writing a prescription.

Targeted vs universal availability

There was extensive discussion around who should receive naloxone—should everyone (universal prescribing) or should only certain (targeted) populations? Researchers agree that individuals at risk can be classified as having a relative risk of overdose or an absolute risk of overdose and that both would need to be taken into account in any targeted program.

- Obvious **targeted** populations would be patients on chronic pharmaceutical opioids for pain, persons who inject opioids, those with diagnosed substance use disorders, persons who have overdosed previously, and prisoners with an opioid use history who are soon to be released (and whose tolerance is low).
 - Generally, other indicators of increased risk, indicating that a person might be targeted for co-prescribing, include *high* opioid dose, longer duration of treatment, larger supplies of therapy, concomitant benzodiazepine prescriptions, getting controlled substances from multiple providers or multiple pharmacies, some types of mental health disorders, and underlying respiratory conditions.
- **Universal** co-prescribing of naloxone can serve many goals. In a recent research project in San Francisco, preliminary findings indicated that patients are appreciative of naloxone prescriptions; pharmacists and prescribers strongly favor prescribing naloxone to patients on opioids; and naloxone seems to help providers engage patients in a dialogue about opioid safety.
 - When providers are advised to offer naloxone to all patients on opioids, they automatically self-select those they believe are at higher risk for overdose.
 - Universal co-prescribing of naloxone could help reach those individuals typically not included in research projects on how to identify persons at risk. These individuals include, for example, children and teenagers who might accidentally or intentionally gain access to and overdose on an opioid drug prescribed to others.
- Pricing is critical in discussions around targeted vs universal coverage and may limit the ability of programs or health systems to provide universal coverage.

V. The Importance of Training in Naloxone Use

There was broad agreement that training or instruction is needed to be able to use naloxone successfully. Training should cover issues such as how to identify an overdose, how to use the delivery device, how to maintain respiratory integrity during and after naloxone administration, and that those who administer the naloxone should stay with the patient until emergency personnel arrive. A number of states have launched programs to train persons receiving naloxone as well as trainers who can train others. Several programs to educate pharmacists in the use of naloxone are underway.

- Even though a number of good training curricula exist, they tend to be tailored to specific topics (e.g., injectable vs intranasal use; how best to maintain respiratory integrity). SAMHSA is developing a standardized model overdose prevention education curriculum.
 - It is critical that trainings and the programs that deliver them are designed to eliminate active or inadvertent biases against drug users or their families.
- SAMHSA also launched the ***Opioid Overdose Prevention Challenge***, a competition with a prize to develop a computer application that builds on the toolkit.

- Rhode Island has assembled a list of best practices—and they have doubled their naloxone distribution through a variety of methods and programs.
 - Trainings should target specific groups, including, for example, illicit drug users, health care professionals, pharmacists, emergency room bedside coaches, or addiction treatment providers.
 - Place-based training (e.g., specific to high-risk locations like parks, certain bars, parts of town, etc.) is also recommended.
 - A 2013 statewide pharmacy-based naloxone training program was launched in Rhode Island via a collaborative pharmacy practice agreement. This model involves pharmacists receiving overdose prevention education, which qualifies them to initiate a prescription for naloxone or honor a request for naloxone directly from a patient or caregiver.
 - The Rhode Island non-profit NOPE-RI trained 66 credentialed trainers in overdose prevention, naloxone administration, and the Good Samaritan law. These trainers are training others, mostly police and emergency personnel.
- Since 2008, Massachusetts has funded community coalitions using SAMHSA block grants with support from the State Bureau of Substance Abuse Services, and the state recently launched a pharmacy training program modeled after the program in Rhode Island.
- Community coalitions can add real value by providing another source of advocacy, outreach, and training to support programs in development.
- Partnering with treatment providers is crucial because their patients may be at greater risk of overdose.

VI. Use by EMS, Police, and Fire Departments

As first responders, emergency medical service (EMS) personnel, police, and fire departments play a critical role in responding to life-threatening emergencies. In 2013, according to the database that captures EMS activities (NEMSIS), 113,153 patients received naloxone through EMS.

- Barriers to naloxone use by EMS, police, and fire departments remain. Coordinating these community services is critical.
 - State and local laws and regulations vary with respect to who may carry naloxone. There are four levels of providers (emergency medical response, emergency medical technician (EMT), advanced EMT, and paramedic), with paramedics receiving the most training on different drugs.
 - In some locations, only paramedics can carry naloxone. In half the states, basic EMTs cannot administer naloxone (even though there is no particular evidence of EMTs using naloxone improperly).
 - It is estimated that police arrive before EMS 80% of the time (sometimes, EMS cannot enter a house until law enforcement arrives). As a result, police administration of naloxone is very important. Yet, in some locations, local health directors have stated that law enforcement personnel are not allowed to carry naloxone.

- Liability issues remain due to lack of consistency and clarity of laws and policies. In South Carolina, a naloxone law, but not a Good Samaritan law, related to naloxone was passed. Research indicates that no liability lawsuits against prescribers have been brought to date.
- It can be difficult to find a prescriber who is willing to write a standing order.
- The National EMS [Scope of Practice Model](#), developed by the National Highway Traffic Safety Administration, serves as the overall guidance for basic EMTs to administer medicine.¹² However it currently does not include administration of naloxone. Plans are to begin an update in 2016, and including naloxone will be one of the considerations.
- Rural areas face substantial barriers to naloxone use.
 - Approximately 80 percent of the land mass in the United States is rural. Urban centers, however, have about 80 percent of the EMS workforce.
 - Rural areas can face numerous obstacles to quick response, including geography, long distances, low population density, call volumes, and lack of availability of training and education for EMS personnel. Many communities have only volunteer fire departments.
 - Not all EMS are staffed with paramedics—especially in rural areas. There is a need to train more basic EMTs in the use of naloxone, and the focus of additional training should be on rural areas.
- New York State has implemented a pilot to expand naloxone use in rural parts of the state; the pilot includes training. To date, 2,000 EMTs have been trained in naloxone use, and there have been 223 opioid overdose reversals.
- Law enforcement must be involved as naloxone programs are being developed and implemented. New programs to train law enforcement are continually being established.
 - At the time of the meeting, there were approximately 570 law enforcement training programs up and running, mostly along the East Coast, sponsored by the Harm Reduction Coalition. HRC is willing to share their materials, including videos.
 - The Justice Department released its [Law Enforcement Toolkit](#) in October 2014 in response to state and local requests for help and the Attorney General’s directive to explore how to include naloxone in their practices and policies.¹³
 - The Toolkit contains samples and templates such as standard operating procedures and training materials that agencies could adopt and make their own.
 - Users of the Toolkit can also obtain assistance with training or in identifying presenters (funding is available to support short-term requests).
- A number of funding options are available for start-up programs.

¹² See the *Scope of Practice Model* at <https://www.nremt.org/nremt/downloads/Scope%20of%20Practice.pdf>. Accessed, October 2015.

¹³ This toolkit is available at <https://www.bjatraining.org/tools/naloxone/Naloxone-Background>. Accessed, October 2015.

- HRSA’s Federal Office of Rural Health Policy is making funding available to some rural communities, focusing on the purchase and placement of naloxone, training, and treatment programs in remote areas.
- Funding can sometimes be obtained through state prosecutors, who may be willing to make asset forfeiture dollars available.
- Byrne Justice Assistance grants are formula funding grants to local communities and states.
- The Harold Rogers Prescription Drug Monitoring Program solicitation can fund community and statewide programs (e.g., law enforcement naloxone programs).
- Public health departments can sometimes also provide funding.
- A number of suggestions were made about how to obtain buy-in for state and local naloxone programs.
 - All the stakeholders in a community must come to the table to resolve issues because in the end, this is a community problem that must be dealt with in the community.
 - EMS, law enforcement managers, and top public health officials are especially important. One suggestion was to start with the police. New York State has trained 3,200 New York state troopers in the use of naloxone and has had 73 reversals. North Carolina also has conducted extensive outreach to the law enforcement community with notable successes.
 - Standardization of practices would be very helpful. A place to start might be at the state Offices of Emergency Medical Services.
 - [Getnaloxonenow.org](http://www.getnaloxonenow.org) is a web-based educational site funded by NIH’s National Institute on Drug Abuse.¹⁴ Training modules for bystanders and first responders (e.g., police, fire fighters, and basic EMTs, not paramedics) are available for download.

VII. New Naloxone Products/Formulations

FDA is reviewing two applications for the approval of intranasal versions of naloxone. Representatives of Adapt Pharma and Indivior summarized how their intranasal naloxone devices work and updated meeting attendees on the status of their applications at FDA. FDA presented on the process for moving a prescription product to over-the-counter use (OTC switch) and described a possible new regulatory program currently under consideration at FDA. The pros and cons of making naloxone available OTC were discussed as was the possibility of allowing pharmacists to make naloxone available.

- Community-based organizations face a number of barriers when trying to obtain sufficient amounts of naloxone.
 - Its prescription status is a barrier. A non-profit organization has to have some sort of medical/legal infrastructure (e.g., a prescriber who is willing to work with them) to even

¹⁴ This web page contains extensive information on naloxone and overdose prevention. See <http://www.getnaloxonenow.org/>. Accessed, October 2015.

purchase naloxone because as lay people they cannot sign up for a contract to purchase a pharmaceutical. (Passing standing order legislation would help alleviate this obstacle.)

- Financial barriers are increasing. Funding is seldom dedicated to purchase naloxone, and prices continue to rise.

Over-the-counter availability

- There was some support for FDA changing naloxone's status from prescription to OTC. Under this scenario, naloxone could be made available in the local drugstore for whoever wished to purchase it, with no requirement for a prescription. This approach has a number of advantages, including that patients or their family members could initiate the process themselves, without a prescription, potentially widening distribution. It would also help patients who may feel uncomfortable discussing their situations with their physicians. A number of related issues were considered.
 - An OTC switch is a process governed by FDA regulations, and particular studies would have to be done, for example, to gather data on consumer label comprehension.
 - To qualify for OTC use, it must be demonstrated that it would be easy to use naloxone without the guidance of a medical professional (a "learned intermediary"). It must also be demonstrated that the user can correctly diagnose the condition.
 - Usually, the application holder requests a switch from prescription to OTC use. An outside party could also do that through the petition process, but the petitioner must provide a full development program and complete data to support the switch. No outside party has so far produced data to support such a switch.
- Other drawbacks were noted.
 - A new label needs to be developed and tested (i.e., additional studies, some involving 500 to 600 individuals).
 - Current OTC labels are very small and may not be able to contain all of the information needed for a naloxone product (e.g., how to recognize an overdose, adverse effects).
 - OTC products typically do not qualify for medical insurance reimbursement.
 - There is concern that making naloxone available OTC and not maintaining the distribution approaches through community-based organizations might limit naloxone availability to the population that needs it most free of charge.
 - In 2015, Pennsylvania passed Act 139, allowing third-party prescribing (e.g., to potential witnesses, police, firefighters, staff of substance use treatment programs, and staff of homeless shelters). Physicians can now prescribe by standing order so a physician doesn't have to be present for training and dispensing. Broad immunity from liability for prescribers and for those who administer naloxone is also included. This Act has resulted in dramatic increases in availability (e.g., naloxone was provided to 457 people in the first 5 months of 2015 compared to 157 in all of 2014) and in reversals (104 so far this year).
 - Some questioned whether illicit drug users would feel comfortable going into the pharmacy to purchase an OTC product.

Possible new FDA regulatory framework

- FDA is considering a new regulatory framework, the Nonprescription Safe Use Regulatory Expansion program (NSURE).
 - NSURE could allow the use of innovative technologies (e.g., smart phone apps, computer kiosks at the point of purchase, vending machines, or websites) to help educate consumers about issues related to novel switch programs.
 - The framework for this new program is still in development, and it will likely take several years before it is in place.

Role for pharmacies

- Could pharmacies play a larger role in making naloxone more available?
 - A variety of approaches are being implemented at pharmacies (e.g., collaborative practice agreements with physicians, state-wide naloxone protocols allowing pharmacists to prescribe naloxone, authority to distribute without a prescription). Rhode Island and Massachusetts both have implemented similar programs.
 - The Drug Policy Alliance has partnered with the California Pharmacy Association to co-sponsor a bill to create pharmacy naloxone access. However, legal, policy, and cost barriers often remain, and approaches vary from state to state.
 - Pharmacies can suffer when reimbursement rates fail to keep up with product price increases. Washington State has developed model legislation, and something similar to this legislation might help iron out some of the price/reimbursement variability from state to state.
 - Stigma could discourage some pharmacies or pharmacists from selling naloxone to *suspect* individuals. Similarly, prospective purchasers may not feel comfortable purchasing the product in pharmacies.

VIII. *Measuring Progress and Impact*

- It is important to have as much evidence as possible to inform policy decisions.
- The VA system is studying the impact of education and training regarding opioid overdose prevention and recognition, opioid overdose rescue response, and the distribution of naloxone kits for outpatient administration of opioid reversal.
 - Outreach to prescribers, pharmacists, and others in the VA system and tracking of kit offers and distribution, reversal reports, and follow-up treatment takes place via electronic communication and is stored in the VA data warehouse.
 - Multiple pilots are under way to educate and inform prescribers (e.g., focus groups, visits by VA *detailers* who can help identify patients with increased risk for overdose and plan intervention strategies).
- An important area of additional research is what happens after an overdose reversal. Are referrals being made to emergency care or drug treatment?
- A lot of research is underway around community-based naloxone distribution, especially around the impact of increased education on overdose and knowledge of, and skills at, using naloxone. For example, John Strang (U.K.) described a randomized trial under way in the U.K., the N-ALIVE

prison release trial, which examined distribution of naloxone to prisoners upon their release. Although the researchers now question whether the primary outcome was well chosen and all data have not been analyzed, the program has succeeded in expanding the use of naloxone among the study population.¹⁵

- Many studies are descriptive, so it will be important going forward to do more rigorous studies. Needs include:
 - Baseline data, control or comparison groups, randomization, adequate statistical testing, larger sample sizes, longitudinal data, and accounting for multiple interventions
 - Qualitative studies to understand how different policies and programs are being implemented
 - Research to understand how best to reach different types of opioid-using populations and the different types of responders currently involved in naloxone provision
 - Assessments of trends in availability, cost, and introduction of new products (e.g., how these factors could change the dynamics of implementation, patient and provider behaviors, and health outcomes)
 - Best practices in implementation of naloxone programs and their uptake
 - Quantitative studies to measure impact on outcomes
 - Studies of people who are receiving opioids for pain with no other histories of substance abuse disorders to be able to understand the impact in various populations (the vast majority of available research now looks at heroin users)
- Data sources can be a challenge. Poison control data are useful, but sometimes hard to access. State-based surveillance systems can provide data, including EMS or pre-hospital data, emergency department data, and data from PDMPs.
- In addition to data, it is important to develop standard definitions and standardize the methods and approaches used to identify specific activities and impacts on health outcomes.

At the end of the two-day meeting, Kimberly Jeffries Leonard, Deputy Director, Center for Substance Abuse Treatment, SAMHSA, provided closing comments. She praised the successes to date and underscored SAMHSA's continued support.

IX. General Conclusions

- There was broad general agreement among meeting participants and attendees that naloxone should be made widely available to persons at risk for overdose and to those who might witness an overdose.
- The number of states with programs that support overdose prevention and treatment has greatly increased since 2012. Nevertheless, many states and communities still lack programs to make

¹⁵ John Strang (U.K.) describes this study in detail in the day-one transcript, beginning on page 77.

naloxone and treatment follow-up available—rural areas where resources may be geographically distant face special barriers. Ensuring that multiple methods of delivery are available will help ensure that naloxone reaches the many populations at risk.

- A large national educational effort would contribute substantially to informing the U.S. public about the risks of overdose, the availability of naloxone and guidance for use, the causes of addiction disease, and treatment options. Such a program could also help sustain and build more of the momentum gathered since the FDA workshop on naloxone in 2012.
- There was broad support for co-prescribing naloxone, with some supporting universal co-prescribing and others recommending a more risk-based approach. National recommendations on who should receive naloxone would be useful.
- A new distribution model may be needed. The cost of naloxone is preventing some programs from initiating or expanding opioid overdose prevention efforts. Some presenters recommended specific federal budget allocations via state block grant programs and other state-based initiatives to increase access to naloxone through community-based programs.
- Training in the use of naloxone and addiction treatment options should be part of any program to make naloxone available.
- More standardization within and among the states with regard to naloxone use is needed (e.g., Good Samaritan laws, the role pharmacists can play, broader EMT training and use, immunity laws, and laws to allow wider naloxone access to laypeople).
- The policy environment around overdose prevention and naloxone use is rapidly changing. Rigorous research using standardized approaches and definitions is critical to inform policy development and implementation.
- Continued collaboration among all stakeholders is critical for achieving additional progress.



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

MEMORANDUM

DATE: September 2, 2016

FROM: Yun Xu, Ph.D.

TO: Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Clinical Pharmacology Background, October 5, 2016 AADPAC/DSaRM Meeting to Naloxone Products

Clinical Pharmacology Background

Naloxone antagonizes opioid effects by competing for the same receptor sites. Following parenteral administration, naloxone is rapidly distributed in the body. Plasma protein binding is relatively weak. Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk. Naloxone is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucuronide as the major metabolite. In one study the half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). After an oral or intravenous dose, about 25-40% of the drug is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours [Narcan (naloxone hydrochloride injection; NDA 16636) label, available at

http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/016636s052s054lbl.pdf].

Narcan (naloxone hydrochloride injection; NDA 16636) was the only naloxone product approved for emergency treatment of known or suspected opioid overdose under an NDA until the recent approvals of Evzio (naloxone hydrochloride Auto-injector; NDA 205787) and Narcan Nasal Spray (naloxone hydrochloride; NDA 208411). The injectable Narcan product has been discontinued from marketing; however, the Agency determined that it was not withdrawn for

reasons of safety or effectiveness (74 FR 22751). Several generic versions of Narcan injection (NDA 16636) are available on the market.

The Narcan injection (NDA 16636) label recommends an initial dose of 0.4 mg to 2 mg for intravenous, intramuscular and subcutaneous administration, followed by repeated doses up to 10 mg for emergency treatment of known or suspected opioid overdose in adults. The minimal naloxone dose or exposure that is clinically effective is unclear, and probably depends on multiple factors, such as type and dose of opioid causing the overdose, route of naloxone administration, etc. However, it is not feasible to design a clinical study to determine the minimal effective naloxone dose because it is not ethical to administer opioids to healthy subjects in order to cause an opioid overdose. Since NDA 16636 is already approved for treatment of this life-threatening condition, there are also logistical and ethical issues associated with evaluating efficacy of new naloxone products in patients with opioid overdose, which could result in death without timely and adequate treatment. Therefore, for development of new naloxone products to treat opioid overdose, the Agency has said that the new naloxone products can be approved by relying on the Agency's previous findings of safety and effectiveness for the previously approved Narcan injection product (NDA 16636).

To rely on the Agency's previous findings of efficacy and safety for NDA 16636, a scientific bridge via a relative bioavailability (BA) study between the new naloxone product and the approved Narcan injection product (NDA 16636) is required. The study should be a randomized, cross-over pharmacokinetics study in healthy subjects 18 years of age and older with adequate sample size. Both the new naloxone product (test) and approved product (reference) must be administered under the labeled recommended dose and route of administration. An adequate wash-out period is needed between treatments. Blood sampling must adequately capture the entire pharmacokinetic (PK) profile, especially for the early onset-of-action phase. To allow for characterization of naloxone plasma concentrations in the early phase, an adequate number of blood samples should be collected in the first thirty minutes after administration. Free (unconjugated) naloxone concentration must be measured for PK analysis.

Pharmacokinetic parameters including peak exposure (C_{max}), time to peak exposure (T_{max}), total exposure including area under the plasma concentration time curve from time zero to last time point with a measurable concentration (AUC_{0-t}), area under the concentration time curve from time zero to time infinity (AUC_{0-inf}), and half-life ($t_{1/2}$) should be calculated. Because overdose may lead to apnea, onset of naloxone action is critical if the brain is to be spared permanent hypoxic injury. The current FDA guidance on bioavailability and bioequivalence studies recommends the use of partial AUC to assess the onset of therapeutic effect. Therefore, partial AUC of early time points should also be compared to assess onset of naloxone effect if the test product shows lower naloxone concentration to the reference at early time points. Although demonstrating bioequivalence is not required, a bioequivalence approach is recommended to analyze C_{max} and AUCs.

The goal of this approach required by the Agency is to demonstrate that the new test product matches or exceeds the systemic naloxone exposure to the reference product by comparing the PK parameters of C_{max}, T_{max} and AUCs. Since onset of action is critical, it should be emphasized that, even if the test product shows comparable or higher C_{max}, AUC_{0-t} and AUC_{0-inf}, it must be demonstrated that the naloxone levels are comparable or higher to the reference product during the early phase after dosing by comparing partial AUCs.

Refer to “*Draft Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations*” available at

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf>, and “*Guidance for industry: Statistical Approaches to Establishing*

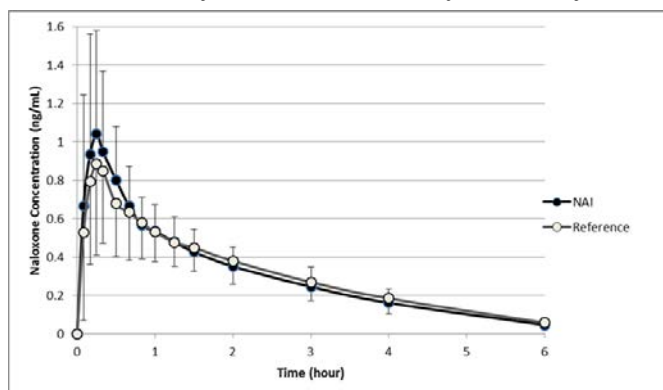
Bioequivalence” available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070244.pdf> regarding study design and data analysis.

Two naloxone products were approved recently for the treatment of opioid overdose; Evzio (naloxone hydrochloride Auto-injector; NDA 205787) and Narcan Nasal Spray (naloxone hydrochloride, NDA 208411). The recommended initial dose is one injection (0.4 mg) for the auto-injector, and one intranasal spray (4 mg) for the Nasal Spray. If the desired response is not obtained after 2 or 3 minutes, another dose may be administered. Both products relied on the Agency’s previous findings for Narcan injection (NDA 16636) by conducting a relative bioavailability study. Since NDA 16636 has been discontinued, generic products of NDA 16636 were used as reference products in the studies.

For NDA 205787, the Applicant conducted a randomized, 2-period, cross-over study in 30 healthy subjects to compare the PK between a single injection of 0.4 mg naloxone HCl using the new auto-injector product (Evzio) and the reference product using a standard syringe into the mid-anterolateral thigh. The injection was either subcutaneous or intramuscular based on the depth of fat under the skin and overlying the muscle and the needle length. The mean naloxone plasma concentration-time profiles are shown below.

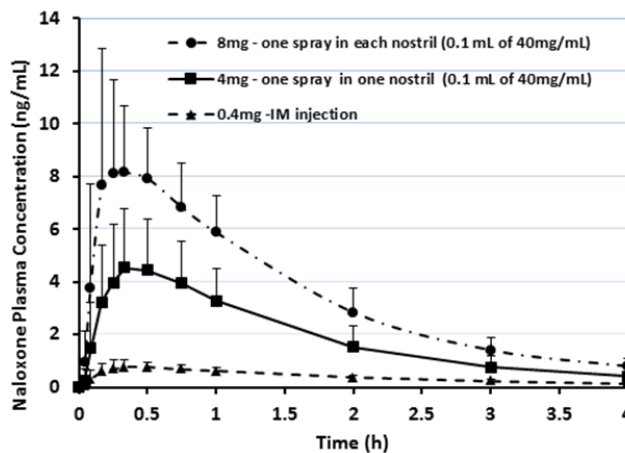
Figure 1: Mean naloxone plasma concentration-time profiles following the administration of naloxone auto-injector (NAI) and reference injection both at a 0.4 mg dose (N = 30)



The mean naloxone plasma concentration-time profiles between Evzio and the reference are almost superimposed except for a slightly higher C_{max} value for Evzio. Median T_{max} and mean half-life were similar for Evzio and the reference product (0.25 h vs. 0.33 h, and 1.28 h vs. 1.36 h). The 90% CIs of the geometric mean ratios for naloxone AUC_{0-t} and AUC_{0-inf} of Evzio to the reference product were within the bioequivalence limits of 80 to 125%. The C_{max} was 15% greater for Evzio compared to the reference product with a geometric mean of 1.15 and 90% CI of (0.97, 1.37).

For NDA 208411, the Applicant conducted a randomized, 5-treatment, cross-over study in 30 healthy subjects to evaluate the pharmacokinetics of two doses of Narcan Nasal Spray (i.e., 4 mg [one spray in one nostril] and 8 mg [one spray in each nostril]) in comparison to the reference naloxone product given intramuscularly at 0.4 mg. Two doses of another intranasal naloxone using a not to-be-marketed formulation were also evaluated in this study. Narcan Nasal Spray was administered with the subject in a fully supine position. The reference naloxone product was administered intramuscularly as a 0.4 mg dose single injection. The mean naloxone plasma concentration-time profiles are shown below.

Figure 2: Mean naloxone plasma concentration-time profiles following administration of one Narcan Nasal Spray in one nostril (i.e., 4-mg dose), one Narcan Nasal Spray in each nostril (i.e., 8-mg dose), and the reference 0.4 mg injection (N=29)



Median T_{max} values were 0.50 hour and 0.38 hour respectively for Narcan Nasal Spray and the reference product, and the mean half-life values were 2.08 hour and 1.24 hour respectively. Both Narcan Nasal Spray doses demonstrated higher naloxone concentrations than the reference product at every time point. Compared to the reference product 0.4 mg intramuscular injection, Narcan Nasal Spray exhibited 5.5-fold (90% CI of 464% to 665%) C_{max}, 4.7-fold (90% CI of 418% to 527%) AUC_{0-t}, and 4.6-fold (90% CI of 412% to 519%) AUC_{0-inf} values for the 4 mg dose; and 11-fold (90% CI of 925% to 1320%) C_{max}, 8.9-fold (90% CI of 793% to 999%) AUC_{0-t}, and 8.8-fold (90% CI of 783% to 985%) AUC_{0-inf} values for the 8 mg dose.

The relative bioavailability study demonstrated that the naloxone levels achieved with 4 mg Narcan Nasal Spray are approximately five times that of 0.4 mg naloxone given intramuscularly. This exposure is likely to fall well within the doses recommended in the approved labeling of the reference product, which recommends up to a 2 mg initial dose and repeating the dose every two to three minutes up to a total dose of 10 mg.

Pharmacokinetics in Pediatrics

It is not feasible to conduct pharmacokinetic (PK) studies in adults or pediatric patients with opioid overdose due to its life-threatening nature and ethical and logistical considerations. In addition, pharmacokinetic studies in healthy children are not allowed by the Agency due to the fact that there would be no benefit to the participant and administration of the investigational product presents greater than minimal risk. Therefore, the PK information for naloxone in the pediatric population is very limited.

Two publications from the 1980s evaluated naloxone pharmacokinetics in newborns. Moreland *et al* (*Br J Clin Pharmacol.* 1980 Jun;9(6):609-12.) studied the naloxone pharmacokinetics in newborns within 1 minute of birth. After intravenous administration via the umbilical vein of 35 (n=6) and 70 (n=6) microgram dose, peak levels of 4-15 ng/ml and 9-20 ng/ml, respectively were reached in 5-40 minutes and the mean plasma half-life after both doses was 3.1 ± 0.5 h. Peak levels of 7-35 ng/ml were reached 0.5 to 2 h after intramuscular administration of 200 microgram (n=17). The labeling for Narcan injection (NDA 16636) states “In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours”, which is likely resulting from this publication.

Stile *et al* (*Dev Pharmacol Ther.* 1987;10(6):454-9.) studied naloxone PK by intravenous bolus injection in ten premature newborns with a mean birth weight of 1328 ± 402 g and a gestational age of 29.4 ± 2.8 weeks at an age of 4.5 ± 3.2 days of life. It is noted that the naloxone dose is not consistent in this publication since the abstract section states 0.4 mg/kg while the drug administration section states 0.04 mg/kg. Based on an abstract (*Pediatric Research* (1984) 18, 161A–161A) by the same group on the same research topic, it is likely 0.04 mg/kg was dosed. The mean naloxone peak levels of 18.7 ± 4.2 ng/mL were observed at 5 minutes, the first blood sampling time point after dose; and a half-life of 70.5 ± 35.2 min was reported. The author also states that further analyses of PK parameters show that the volume of distribution significantly correlates with body weight.

The naloxone half-life values are different between the two publications described above. It is not clear what accounts for this difference, and it is possibly due to incomplete capture of the elimination phase. Naloxone is metabolized in the liver primarily by UDP-glucuronosyltransferase (UGTs) to glucuronide conjugates. Krekels *et al* (*Curr Drug Metab.* 2012 Jul;13(6):728-43) reported that the onset of UGT expression and activity occurs after 20 weeks of gestation with a boost in expression and activity occurring in the first week of life.

Maturation rates vary between the UGTs, but may well extend beyond the age of two years. Therefore, it is very likely that naloxone has a longer elimination half-life in newborns compared to adults.

It was also reported that the volume of distribution significantly correlated with body weight in newborns. As naloxone is rapidly absorbed after injection or inhalation, volume of distribution will play a major role on the C_{max} value. Therefore, for the same fixed-dose (i.e. not body-weight based), it is very likely that a pediatric subject with lower body weight will have a higher C_{max} value.



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To: Division of Anesthesia, Analgesia, and Addiction Products

Subject: Maternal Health, Neonatal-Perinatal Medicine, and
Pediatric Consultations: Background Information for
Naloxone Advisory Committee to be held October 5, 2016

I. Background

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AC) and the Drug Safety and Risk Management AC is scheduled for October 5, 2016. The committees will be asked to discuss naloxone products intended for use in the community, specifically the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in the community setting. The committee members will also be asked to discuss criteria prescribers can use to select and prescribe the most appropriate dose in advance of an opioid overdose event in the setting of availability of multiple doses, and how labeling can be developed to inform prescribers' decisions.

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has consulted both the Maternal Health and Pediatric teams in the Division of Pediatric and Maternal Health (DPMH) as well as the Office of Pediatric Therapeutics to assist in preparation for this meeting by providing maternal health, neonatal, and pediatric considerations to inform the joint AC discussion. This memorandum is a collaborative review.

II. Naloxone Use in Pregnant and Breastfeeding Women

There are no data on the appropriate dosing of naloxone intended to reverse the effects of life-threatening opioid overdose in pregnant and breastfeeding women; however, current Substance Abuse and Mental Health Services Administration (SAMHSA) guidelines on the treatment of opioid overdose in pregnant women include a recommendation to use “the lowest dose to maintain spontaneous respiratory drive to avoid triggering acute opioid withdrawal, which may cause fetal distress.”¹ Follow-up monitoring of the mother and fetus should be performed. The effects of acute withdrawal on the fetus are not well understood, and more research is needed in this area.^{2,3} Based on studies in pregnant mice and rats that were administered naloxone by injection at doses up to 1,000 times the human dose, there were no adverse effects on the fetus.⁴

¹ Substance Abuse and Mental Health Services Administration . SAMHSA Opioid Overdose Prevention Toolkit. HHS Publication No. (SMA) 13-4742. Rockville, MD. Substance Abuse and Mental Health Services Administration, 2013.

² Bell J, Towers CV, Hennessy MD, Heitzman C, Smith B, Chattin K. Detoxification from opiate drugs during pregnancy. *Am J Obstet Gynecol*. 2016 Mar 17. [Epub ahead of print]

³ McCarthy, JJ, Terplan M. Detoxification from opiates during pregnancy: stressing the fetal brain. Letter to the Editor in response to Bell J, Towers CV, Hennessy MD, Heitzman C, Smith B, Chattin K. Detoxification from opiate drugs during pregnancy. *Am J Obstet Gynecol*. 2016 Mar 17. [Epub ahead of print] 2016 June 2. .[Epub ahead of print]

⁴ Naloxone hydrochloride Labeling 2013. Daily Med.
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=76f7eee1-d524-43a4-a868-ffa9f29638a6>

There are no studies of naloxone administered for opioid overdose in pregnant women; however, there are no reports in the medical literature that have reported adverse events on the fetus.

The administration of naloxone to a breastfeeding woman for management of overdose is unlikely to pose a risk to the breastfeeding infant as naloxone is poorly absorbed orally.^{5,6}

III. Neonatal Population: See Office of Pediatric Therapeutics review in Appendix C.

IV. Other Pediatric Patients

A. Acute Opioid Overdose in the U.S. Pediatric Population

Acute opioid overdose in pediatric patients is a preventable public health problem. Increased availability of effective naloxone drug products has the potential to reduce morbidity and mortality in pediatric patients who acutely overdose on opioids both inside and outside of controlled medical settings.

Acute opioid overdose is most likely to occur due to abuse among adolescents because recreational use of opioids has been increasing in this pediatric age group. In contrast, accidental opioid ingestion is the most likely cause of acute opioid overdose in younger pediatric patients, particularly those less than 6 years of age, in whom opioid ingestion typically occurs from exposure to prescription opioids or illicit drugs in the home environment.^{7,8}

Prescription opioids such as morphine, diphenoxylate hydrochloride, fentanyl, methadone, and buprenorphine have been implicated in causing acute overdose in young pediatric patients.^{9,10,11,12,13,14,15} Pediatric methadone and buprenorphine exposures are particularly

⁵ Hale, Thomas. Medications and Mothers' Milk 2014. Amarillo, Texas. Hale Publishing

⁶ Lactmed <https://www.toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~eMzGB3:4>

⁷ Martin TC and Rocque M. Accidental and Non-Accidental Ingestion of Methadone and Buprenorphine in Childhood: A Single Center Experience, 1999-2009. Current Drug Safety 6: 12-16, 2011.

⁸ Hayes BD, Klein-Schwartz W, and Doyon S. Toxicity of Buprenorphine Overdoses in Children. Pediatrics 121(4): e782-e786, 2008.

⁹ Lewington LE, Shaffer C, Ornstein A. Paediatric Methadone Ingestions: An Under-Recognized Form of Child Maltreatment? Paediatric Child Health 19(3): 139-140, 2014.

¹⁰ Martin T and Rocque MA. Accidental and Non-Accidental Ingestion of Methadone and Buprenorphine in Childhood: A Single Center Experience, 1999-2009. Current Drug Safety 6(1): 1-5, 2011.

¹¹ Behrman A and Goertemoeller S. A Sticky Situation: Toxicity of Clonidine and Fentanyl Transdermal Patches in Pediatrics. Journal of Emergency Nursing 33: 290-293, 2007.

concerning because use of a single low dose of naloxone may be inadequate to provide continuous antagonism of the effects from overdose with either of these two long-acting opioids. Data from the American Association of Poison Control Centers (AAPCC) show that the number of methadone exposures tripled and the number of buprenorphine exposures increased 900% in pediatric patients less than 6 years of age from 2000 to 2008.¹⁶ These AAPCC data also report that 20 deaths related to methadone exposure and no deaths related to buprenorphine exposure occurred in patients less than 6 years of age during the same 8-year time period. The upward trend in pediatric household methadone and buprenorphine exposures appears to be concordant with the increased prescribing of methadone and buprenorphine drug products for outpatient treatment of opioid addiction and chronic pain in the United States. From 2007 to 2011, opioids accounted for the largest number of emergency department visits and subsequent hospitalizations due to unsupervised ingestions of prescription drugs (17.6% of 9,490 estimated emergency hospitalizations) in patients less than 6 years of age, and buprenorphine was the active ingredient most commonly implicated in the emergency hospitalizations.¹⁷

B. Efficacy and Dosing Considerations for Naloxone Hydrochloride Drug Products

The pediatric efficacy of naloxone HCl was established with approval of Narcan (naloxone HCl for injection) in 1971 and time and extent of use since initial U.S. approval further support naloxone's effectiveness in reversing opioid effects in pediatric patients.

Although limited clinical data can be found in the Narcan new drug application (NDA) to support the approved pediatric dosing recommendations, controlled efficacy trials are challenging to conduct in all age groups, not just pediatrics, for both ethical and logistical reasons. Recognizing these challenges, FDA established a plan for the clinical development of

¹² Teske J, Weller JP, Larsch K, et al. Fatal Outcome in a Child after Ingestion of a Transdermal Fentanyl Patch. *International Journal of Legal Medicine* 121(2): 147-151, 2007.

¹³ Bakovic M, Nestic M, Mayer D. Death by Band-Aid: Fatal Misuse of Transdermal Fentanyl Patch. *International Journal of Legal Medicine* 129(6): 1247-1252, 2015.

¹⁴ McCarron MM, Challoner KR, Thompson GA. Diphenoxylate-Atropine (Lomotil) Overdose in Children: An Update (Report of Eight Cases and Review of the Literature). *Pediatrics* 87(5): 694-700, 1991.

¹⁵ Gill AM, Cousins A, Nunn AJ, et al. Opiate-Induced Respiratory Depression in Pediatric Patients. *Pediatrics* 30: 125-129, 1996.

¹⁶ Boyer EW, McCance-Katz EF, Marcus S. Methadone and Buprenorphine Toxicity in Children. *The American Journal on Addictions* 19: 89-95, 2009.

¹⁷ Lovegrove MC, Mathew J, Hamp C, et al. Emergency Hospitalizations for Unsupervised Prescription Medication Ingestions by Young Children. *Pediatrics* 134: e1009-e1016, 2014.

novel naloxone drug products relying on a pharmacokinetic (PK) standard in lieu of conducting efficacy trials. This clinical development plan was publicly shared in 2012¹⁸ and again in 2015¹⁹ and requires novel naloxone drug products to demonstrate comparable or greater bioavailability to an approved naloxone dose and route of administration in healthy adult volunteers. The novel naloxone drug product must match or exceed the PK profile of the approved naloxone product, especially during the early critical period of opioid overdose when prolonged apnea can lead to permanent hypoxic brain injury or death. The key PK parameters include the peak plasma concentration [C_{\max}], time to C_{\max} [T_{\max}], and systemic exposure as measured by the area under the concentration time curve [AUC] during the first few minutes post-dosing.

The PK studies supporting approval of novel naloxone drug products are conducted in adults and do not typically rely on PK evaluation in pediatric patients. While the PK profiles of drugs are generally considered to be similar between adults and adolescents,²⁰ the PK profile may be considerably different in younger pediatric patients and may require them to receive higher naloxone doses than adults. At least two publications^{21,22} describe safe provision of naloxone infusion for acute opioid overdose in pediatric patients less than 3 years of age at rates higher than those reported in adults.²³ These publications suggest that a single low dose of naloxone may be inadequate to provide continuous antagonism of the effects of overdoses of long-acting opioids.

C. Currently Approved Naloxone Hydrochloride Drug Products

Two novel naloxone HCl drug products, Evzio Auto-Injector and Narcan Nasal Spray, have met FDA's PK standard for approval to date. Evzio was the first approved naloxone drug product intended for use in the community setting by individuals who are not medically trained or first

¹⁸ Transcript from April 12, 2012 Public Workshop on Role of Naloxone on Opioid Overdose Fatality Prevention: <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM304621.pdf>; accessed August 6, 2016.

¹⁹ Exploring Naloxone Uptake and Use Public Meeting July 1 and 2, 2015: <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM469456.pdf>; accessed August 6, 2016.

²⁰ Momper JD, Mulugeta Y, Green DJ, et al. Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007. *JAMA Pediatrics* 167(10): 926-932, 2013.

²¹ Gourlay GK and Coulthard K. The Role of Naloxone Infusions in the Treatment of Overdoses of Long Half-Life Narcotic Agonists: Application to Nor-Methadone. *British Journal of Clinical Pharmacology* 15: 269-272, 1983.

²² Lewis JM, Klein-Schwartz W, Benson BE, et al. Continuous Naloxone Infusion in Pediatric Narcotic Overdose. *American Journal of Diseases of Children* 138(10): 944-946, 1984.

²³ Bradberry JC and Raebel MA. Continuous Infusion of Naloxone in the Treatment of Narcotic Overdose. *Drug Intelligence and Clinical Pharmacy* 15: 945-950, 1981.

responders. Narcan Nasal Spray was the first approved naloxone intranasal (IN) spray and is intended for use in the community setting by individuals who are not medically trained or first responders. Both products are approved for prescription use in all pediatric ages from birth to 17 years. See Appendix A for a tabular summary of the indications and pediatric dosages for the currently approved naloxone HCl drug products.

Marketing of the innovator naloxone HCl for injection, Narcan, has been discontinued. However, the Agency determined that the innovator was not withdrawn from sale for reasons of safety or effectiveness (74 FR 22751). Multiple generic injectable naloxone drug products are currently available.

No naloxone HCl drug products are currently approved for over-the-counter (OTC) use by either adults or pediatric patients.

The approved pediatric doses for Evzio and Narcan Nasal Spray are fixed-doses equivalent to the approved adult dose. In contrast, naloxone for injection labeling includes weight-based pediatric dosing for known or suspected opioid ingestion. Smaller, incremental fixed doses are described in labeling for reversal of post-operative sedation. Too rapid reversal by administration of a larger than necessary naloxone dose in the post-operative setting may not only dramatically reverse analgesia but also increase blood pressure and induce the undesirable effects of nausea, vomiting, sweating, or circulatory stress. For both indications, labeling states that naloxone HCl for injection may be diluted for intravenous (IV) infusion and the rate of administration should be “titrated in accordance with the patient’s response.” Labeling does not specify if there is a maximum single or daily dose which should not be exceeded in pediatric patients but does specify that if no response is observed in adults after administration of 10 mg of naloxone HCl, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned.

Labeling instructions for Evzio and Narcan Nasal Spray emphasize the importance of seeking emergency medical services (EMS) as soon as possible after administering the first dose and that additional supportive and/or resuscitative measures may be helpful while awaiting EMS. Contacting EMS is particularly important in pediatric patients with increased body weight or patients who ingest long acting opioids, extended release formulations or partial agonists/mixed agonists/antagonists such as buprenorphine, pentazocine, or methadone. In these settings, there is the likelihood that repeat naloxone doses will need to be administered in order to achieve an adequate response. See Section I. Labeling dosing instructions for both products state that repeat doses at 2 or 3 minute intervals may be required depending upon the amount, type, and route of administration of the opioid being antagonized. Despite these labeling instructions for repeat dosing, administration of more than two consecutive doses are unlikely to be administered since each product is currently packaged to provide two doses only.

For pediatric patients over 1 year of age, Evzio labeling instructions state to administer a fixed, dose of 0.4 mg IM or SC into the anterolateral aspect of the thigh, through clothing if necessary, and seek EMS. For patients less than 1 year of age, the caregiver should pinch the thigh muscle while administering Evzio.

D. American Academy of Pediatrics Committee on Drugs Recommendations

In 1980, the American Academy of Pediatrics (AAP) Committee on Drugs (COD) published a commentary about naloxone use in newborns and recommended using the approved Narcan for injection pediatric dose in newborns.²⁴ The commentary stated that most of the controlled clinical trials to study naloxone's safety and efficacy in treating respiratory depression in narcotic-exposed newborns have been conducted in full-term, healthy infants whose mothers received morphine or meperidine HCl during labor and showed no overt clinical evidence of respiratory or CNS depression at birth. The COD further stated that study endpoints, methods of assessment, and naloxone dosing and route of administration varied across studies, rendering comparisons difficult and study results inconsistent. The COD noted that one controlled study which attempted to evaluate the efficacy of naloxone administered just prior to delivery to reverse potential narcotic-induced respiratory depression was difficult to interpret due to the poorly controlled study conditions.²⁵ Despite the lack of controlled clinical trial data, the COD cited multiple published cases describing successful and safe use of naloxone in treating children with acute opioid overdose and recommended the following:

- Immediate initiation of customary resuscitative efforts in the presence of signs of neonatal depression;
- Naloxone should not be used in lieu of immediate resuscitative measures;
- Reserve naloxone use as adjunctive therapy in selected infants who demonstrate significant depression, who have been exposed to intrapartum narcotics, and who are unable to maintain effective spontaneous ventilation despite other resuscitative efforts;
- Neonatal naloxone dose of 0.01 mg/kg which may be repeated in 3-5 minutes if no immediate response;
- Naloxone should preferably be administered IV in order to obtain an immediate effect;
- Although naloxone may be given IM or SC, absorption via these routes may be erratic and delayed in the stressed and vasoconstricted infant

²⁴ Committee on Drugs: Naloxone Use in Newborns. *Pediatrics* 65(3): 667-669, 1980.

²⁵ Clark RB, Beard AG, Greifenstein FE, et al. Naloxone in the Parturient and Her Infant. *Southern Medical Journal* 69: 570, 1976.

In 1988, the COD updated the recommendations for emergency pediatric drug dosing in which they recommended an IV naloxone dose of 0.01 mg/kg to 0.1 mg/kg with a minimum dose of 0.5 mg in newborns with suspected intoxication with opiates.²⁶ For older children and adolescents, the COD recommended a minimum fixed IV naloxone dose of 2 mg. The COD recommended repeat dosing as needed.

Since the 1988 emergency drug dosing guideline did not include the scientific basis for the COD's recommendation to deviate from the approved Narcan for injection pediatric dosing recommendations, the COD published a clarification statement in 1989.²⁷ In the 1989 statement, the COD recommended an initial IV or intratracheal naloxone dose of 0.1 mg/kg from birth through age 5 years or 20 kg and a minimum fixed dose of 2 mg for those greater than 5 years of age or weighing greater than 20 kg. The COD stated these doses could be repeated as needed to maintain opiate reversal. The COD cautioned that use of the 0.02 mg/mL parenteral naloxone formulations is no longer recommended because of the potential for volume overload especially to small neonates. Rather, the COD recommended use of 0.4 mg/mL or 1 mg/mL parenteral formulations administered via appropriately sized syringes.

In 1990, the COD published an addendum to provide additional scientific rationale for the revised pediatric naloxone dosing recommendations issued in 1988. The COD clarified that the higher dose recommendation was based, in part, on a concern that the 0.01 mg/kg approved dose may not provide optimal opiate reversal in some infants. The COD stated the higher dose is intended to simplify naloxone dosing and provide greater probability of optimal opiate reversal in most patients. The COD supported this statement by referencing a single randomized, double-blind study which evaluated the efficacy of 0.04 mg IV naloxone in 1 mL (n=10) versus 1 mL isotonic saline (n=18) given within 1 minute of birth to term and otherwise healthy newborns born to mothers who had received 100 mg to 300 mg of pethidine during labor.²⁸ Results showed alveolar carbon dioxide tension was significantly lower and alveolar ventilation was significantly higher in the naloxone-treated than saline-treated patients. The COD further cited the lack of naloxone-related adverse effects associated with administration of individual doses up to 0.4 mg/kg in a clinical trial of naloxone use to reverse neonatal birth asphyxia and when given at a constant IV infusion rate of 0.16 mg/kg/hour for 5 days as further support of naloxone's

²⁶ American Academy of Pediatrics Committee on Drugs: Emergency Drug Doses for Infants and Children. *Pediatrics* 81(3): 462-466, 1988.

²⁷ Emergency Drug Doses for Infants and Children and Naloxone Use in Newborns: Clarification. *Pediatrics* 83(5): 803, 1989.

²⁸ Wiener PC, Hogg MIJ, Rosen M. Effects of Naloxone on Pethidine-Induced Neonatal Depression: Part I – Intravenous Naloxone. *British Medical Journal* 2: 228-231, 1977.

safety. The COD reiterated that the IV and intratracheal routes are preferable because absorption of IM or SC routes may be erratic and/or delayed in the patient who is hypotensive, hypoperfused, and/or peripherally vasoconstricted.

The 1990 AAP recommendations for pediatric naloxone dosing have been incorporated into the Pediatric Advanced Life Support (PALS) guidelines.²⁹ The 2005 AHA/AAP Neonatal Resuscitation guidelines recommended consideration of naloxone use for infants born to mothers with a history of opioid exposure within 4 hours of delivery who have persistent respiratory depression even after restoration of heart rate and color by effective positive pressure ventilation.³⁰ However, the updated 2010 guidelines do not recommend naloxone administration as part of initial resuscitative efforts in the delivery room or for newborns with respiratory depression because naloxone's safety and long-term effects are not established.³¹ Rather, the AHA guidelines state heart rate and oxygenation should be restored by supporting ventilation.

E. Basis for Approval of Evzio and Narcan Nasal Spray in Pediatric Patients

The approval of both Evzio and Narcan Nasal Spray was based on results from a single relative bioavailability (BA) study in healthy adult volunteers that was further supported by a human factors validation study in adults and adolescents 12 years of age and older.^{32,33} Relative bioavailability data supporting the approval of Narcan Nasal Spray demonstrated that a 4 mg IN dose is equivalent to a 2 mg IM dose which is the AAP recommended parenteral dose for patients 5 years of age or greater or weighing 20 kg or greater. FDA approved the fixed dose 4 mg IN product to ensure availability of a non-invasive naloxone formulation to provide a life-saving therapeutic option in the full pediatric age range for emergency use in the community setting. No pediatric efficacy or PK data were required, and efficacy data for the previously approved Narcan for injection were leveraged to support the pediatric approval of both products.

²⁹ Kleinman ME, Chameides L, Schexnayder SM, et al. Part 14: Pediatric Advanced Life Support. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 122(Suppl 3): S876-S908, 2010.

³⁰ AHA/AAP Neonatal Resuscitation Guidelines 2010: Summary of Major Changes and Comment on its Utility in Resource-Limited Settings: <http://www.newbornwhocc.org/pdf/NRP2010-Changes.pdf>; accessed August 25, 2016.

³¹ Kattwinkel J, Perlman JM, Aziz K, et al. Part 15: Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 122 (Suppl 3): S909-S919, 2010.

³² Cross Discipline Team Leader Review of NDA 205787 for Evzio (accessed at Drugs@FDA on August 6, 2016).

³³ November 18, 2015 Summary Review of NDA 208411 for Narcan Nasal Spray (accessed at Drugs@FDA August 31, 2016)

The human factors validation study for Evzio was conducted in a total of 40 participants, including 19 adolescents 12 years of age and older, who were asked to deliver a simulated injection without training. Five percent to 26% of the small number of adolescents who participated experienced difficulty with one or more aspects of the labeled instructions. The human factors validation study for Narcan Nasal Spray included 53 participants, including 16 adolescents 12 years of age and older, all of whom were considered to be representative of the intended user group and untrained on the use of the device.³³ All participants were observed to determine if they were able to perform the two critical tasks of inserting the nozzle into the nostril and press the plunger to release the dose in the nose. Success was determined based on the correct completion of both critical tasks. A lower percentage of the adolescent participants correctly completed both critical tasks compared to the adult participants (81.3% [13/16] vs. 94.6% [35/37]).

Caregivers of younger, school-aged children, infants, or newborns were not included in the human factors validation study; their participation may have been useful to ensure the instructions for use were understood, especially given that there was broad agreement at the 2015 public workshop¹⁹ that training or instruction is needed to be able to use naloxone successfully and that training should include how to use the delivery device.

Additional data supplied by the sponsors to support pediatric approval of Evzio and Narcan Nasal Spray primarily consisted of retrospective reviews, case reports, and case series. None were controlled clinical trials. Despite their inherent limitations, the available publications do provide some insight into how naloxone is currently being used in healthcare settings and how the administered doses compare to those recommended in product labeling versus those recommended by the AAP COD. There have been no well-controlled studies on the appropriate dose of naloxone for pediatric patients with acute opioid overdose in different clinical settings.

One retrospective chart review was designed to evaluate the cardiovascular and respiratory responses and any adverse effects associated with IV naloxone use when given as an antidote in pediatric patients with known or suspected opioid-induced overdose as evidenced by central nervous system (CNS) depression, respiratory depression, or both.³⁴ The review included 195 pediatric patients, who received IV naloxone. One group consisted of patients who received naloxone for post-operative reversal of fentanyl-supplemented general anesthesia for different surgical procedures (n=116). Another group (n=79) consisted of patients who were treated with naloxone for known or suspected opioid overdose in the emergency room (ER) (n=52) or for

³⁴ Hasan RA, Benko AS, Nolan BM, et al. Cardiorespiratory Effects of Naloxone in Children. *Annals of Pharmacotherapy* 37: 1587-1592, 2003.

known morphine- or fentanyl-induced respiratory depression in the pediatric intensive care unit (PICU) setting (n= 27). The median (range) initial dose was 0.05 mg (0.01 to 3 mg). The initial naloxone dose used by PICU and ER physicians was substantially higher and in accordance with AAP recommendations than the dose used by anesthesiologists (0.1 mg/kg to maximum of 2 mg vs. 0.01-0.02 mg regardless of body weight). The median (range) total dose was 0.1 mg (0.01 to 7 mg [0.001 to 0.5 mg/kg body weight]). Subjective improvement within 5 minutes of treatment was noted in 71% (139/195) of patients as recorded by the nursing care for the patients. None of the patients in this study developed arrhythmias, hypotension, seizures, emesis, or cardiac arrest after naloxone administration. One 17 year old male developed progressive hypoxia and bradycardia requiring tracheal intubation within five minutes of 2 mg IV naloxone administration by EMS; acute pulmonary edema was subsequently confirmed radiographically. He had been found unresponsive after ingesting unknown amounts of tramadol HCl, phenylpropanolamine maleate, and erythromycin.

Another retrospective case review aimed to determine the prevalence of symptomatic buprenorphine exposure requiring PICU admission in pediatric patients less than 3 years of age at a single academic center from 2007 to 2009, the severity of the associated toxicity, and what clinical interventions were effective.³⁵ Nine cases of opioid toxicity, most commonly presenting with drowsiness or lethargy, were identified involving single-agent exposure to the combination product buprenorphine/naloxone at the child's primary residence. In all 9 cases, an orange residual liquid or a partial pill suggestive of the sublingual formulation was found, suggesting the drug had dissolved in the child's mouth instead of being swallowed. The median (range) age was 22 months (10 months to 33 months). Six patients received IV or IM naloxone at a mean (range) dose of 0.07 mg/kg (0.03 mg/kg to 0.1 mg/kg); 2 patients received their 1st dose by EMS pre-hospital and 4 patients received their first dose in the ER. One patient received an initial IV dose of 0.09 mg/kg and was then placed on an IV infusion at 0.05 mg/kg/hour for 16 hours; the infusion was started because the initial IV bolus dose did not sufficiently reverse the respiratory effects of opioid exposure. Naloxone administration was associated with marked clinical improvement in all cases. The full reversal naloxone dose of 0.1 mg/kg as recommended by the AAP was used in only 3 cases. In the other 6 cases, smaller doses were effective at reversing symptoms.

One case series described five children less than 2 years of age with accidental ingestion of combination tablets containing buprenorphine and naloxone.³⁶ Four of the 5 children were treated with IV naloxone at weight-based doses; two children received close to the labeled initial

³⁵ Pedapati EV and Bateman ST. Toddlers Requiring Pediatric Intensive Care Unit Admission Following At-Home Exposure to Buprenorphine/Naloxone. *Pediatric Critical Care Medicine* 12(2): e102-e107, 2011.

³⁶ Geib A, Babu K, Ewald MB, et al. Adverse Effects in Children after Unintentional Buprenorphine Exposure. *Pediatrics* 118(4): 1746-1751, 2006.

dose (0.072 mg/kg and 0.016 mg/kg) while the other 2 children received close to the AAP recommended initial weight-based dose (0.16 mg/kg and 0.1 mg/kg). The child given the lowest initial starting dose of 0.072 mg/kg subsequently required an IV infusion at a rate of 0.5 mg/hour titrated over 17 hours. All 4 children who received naloxone had reversal of their respiratory depression and recovered uneventfully.

Case reports cited by the sponsors for Evzio and Narcan Nasal Spray included 9 pediatric cases of acute opioid overdose in patients less than 7 years of age; 6 of the 7 patients were less than 3 years of age. Acute opioid overdose in these cases was due to accidental exposure to buprenorphine/naloxone co-formulations (n=5), acetaminophen/codeine co-formulations (n=1), nor-methadone (n=1), fentanyl (n=1), and morphine (n=1). Eight of the 9 patients received naloxone as an IV bolus, IV infusion, or both as part of their medical care. Six received an initial IV naloxone dose consistent with the approved labeling and not the higher dose recommended by the AAP COD. All 9 patients were hospitalized and fully recovered. No naloxone-related adverse events were described. See Appendix B for a tabular summary of these cases.

F. Clinical Considerations Based on Route of Administration

Despite naloxone's established safety margin, there are potential clinical implications with novel naloxone drug products which propose new dosage delivery systems and increase the availability of multiple fixed, non-weight based doses.

The ability of a novel route of administration to deliver the intended dose should be assessed in order to justify use in the entire pediatric age range. Inadequate absorption of naloxone could have serious implications by resulting in lack of the intended effect in pediatric patients requiring immediate reversal of opioid effects. Factors to evaluate include anatomical considerations and optimization of safe, local drug delivery to the intended site.

1. Intranasal Dosage Delivery

From the drug delivery perspective, potential differences in nasal morphology, nasal cavity dimensions, and pattern of IN particle deposition between adults and pediatric patients may not guarantee that IN deposition demonstrated in adults can accurately predict IN deposition in pediatric patients. Both the size and shape of the nasal airways vary significantly with age, and the most dramatic growth in the upper respiratory tract appears to occur in the first five years of life. Young pediatric patients have smaller nostrils, shorter turbinate regions, and narrower nasopharynx than adults. There is some published evidence that these differences in nasal

morphology are also associated with large inter-individual variability in the pattern of deposition of intranasally administered particles among pediatric patients under age 5 years.^{37,38}

Optimization of dosage delivery of IN drugs requires knowledge of the interactions between the formulation, the device, the mode of administration, and patient and/or caregiver technique.³⁹ Demonstration of effective caregiver technique is particularly important because inadvertent swallowing of the drug rather than inhalation is likely to lead to treatment failure given the poor oral bioavailability of naloxone.

Factors to consider that are potentially associated with decreased IN drug absorption include the following:⁴⁰

- Use of a formulation with undesirable pharmacologic characteristics for IN absorption; the highest IN absorption appears to occur with drugs that are characterized by low molecular weight, high lipophilicity, and no net charge at physiologic pH;
- Short duration of drug exposure to the nasal mucosa; epistaxis or a large amount of nasal secretions will reduce contact of the drug with the mucosal surface and reduce the mucosal surface area available for absorption;
- Deposition of the drug in the wrong part of the nasal cavity; this may result in not only reduced absorption but also increased runoff into the posterior pharynx with the potential for subsequent entry into the lungs or oral ingestion.
- Effective IN delivery of the proposed drug may be compromised if the actuator tip is not properly designed for adequate insertion into the nares of neonates and other young pediatric patients. A nasal actuator which is too large to fit in the nostrils of younger pediatric patients might pose concerns regarding accurate dose delivery, and, more importantly, might raise issues of local and ocular safety in young children. Conversely, a nasal actuator fit which is too small may result in low delivery due to drug retention inside the nosepiece, unacceptable variability in dose uniformity, or both.
- Due to the low surface area of the nasal mucosa, IN administration of volumes greater than 200 microliters (μL) may be associated with increased runoff into the pharynx.⁴¹

³⁷ Xi J, Berlinski A, Zhou Y, et al. Breathing Resistance and Ultrafine Particle Deposition in Nasal-Laryngeal Airways of a Newborn, and Infant, a Child, and an Adult. *Annals of Biomedical Engineering* 40(12): 2579-2595, 2012.

³⁸ Xi J, Si X, Zhou Y, et al. Growth of Nasal and Laryngeal Airways in Children. Implications in Breathing and Inhaled Aerosol Dynamics. *Respiratory Care* 59(2): 263-273, 2014.

³⁹ Foo MY, Cheng Y, Su w, et al. The Influence of Spray Properties on Intranasal Deposition. *Journal of Aerosol Medicine* 20(4): 495-508, 2007.

⁴⁰ Del Pizzo J and Callahan JM. Intranasal Medications in Pediatric Emergency Medicine. *Pediatric Emergency care* 30: 496-504, 2014.

Pediatric considerations during the NDA review of Narcan Nasal Spray primarily focused on how the safety and effectiveness of the intranasal route of administration for this product could be assured. Specific concerns raised during the review included the following:

- Improper positioning of the actuator tip could deliver a minimally effective dose in pediatric patients under five years of age given their differences in nasal morphology;
- Administration of the fixed non-weight based dose of 4-mg dose to patients less than 5 years of age could deliver a dose approximately 100-fold higher than what is recommended in Narcan labeling if the full dose is systemically absorbed;
- The potential for IN administration to induce respiratory distress in the youngest patients because of obligate nasal breathing.

Pediatric approval of Narcan Nasal Spray was supported by the demonstration of safe and correct use of the nasal spray device by non-medically trained individuals and on the adequacy of the 4 mg fixed IN dose in providing adequate reversal of opioid effects in all pediatric patients. Given Narcan Nasal Spray's intended use in the community setting, FDA ultimately considered the 4 mg IN dose to be adequate for pediatric use if the product was packaged with two doses so a second dose would be available prior to the arrival of EMS. Since the Narcan Nasal Spray device is flat, with a pinhole delivery, and can therefore be pressed flat against the nostril to deliver the spray, FDA did not require additional studies to demonstrate actuator fit in infants or correct use by caregivers.

2. Fixed Dose Intramuscular Auto-Injection Delivery

Naloxone drug products being developed for auto-injection (IM or SC) must evaluate the potential for the product to over-penetrate the site of injection particularly in the youngest pediatric patients as well as thin or cachectic older pediatric patients and adults. Products intended only for IM use must be evaluated for under-penetration if the product is inadvertently administered into the SC rather than the IM space. Under-penetration of IM delivery may be most likely in obese patients and could be problematic if IM versus SC naloxone delivery results in very different rates of absorption. Recognizing the concerns for under- or over-needle penetration, the Centers for Disease Control and Prevention has issued recommendations to guide clinicians on the use of optimal needle size and site of injection in the context of vaccine delivery.⁴² Similar considerations apply to naloxone drug products intended for IM or SC use,

⁴¹ Grassin-Delyle, Buenestado A, Naline E, et al. Intranasal Drug Delivery: An Efficient and Non-Invasive Route for Systemic Administration. Focus on Opioids. Pharmacology & Therapeutics 134: 366-379, 2012.

⁴² Kroger AT, Sumaya CV, Pickering LK, Atkinson, National Center for Immunization and Respiratory Diseases. "Recommendations of the Advisory Committee on Immunization Practices (ACIP)" Jan. 28, 2011 60(RR02);1-60: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm>; accessed August 12, 2016.

particularly when the product will be used primarily by laypeople. The CDC recommendations state that injection technique is the most important parameter to ensure efficient IM delivery, supporting the need to assess the ability of caregivers of young pediatric patients (e.g. less than 3 years of age) to correctly administer IM naloxone drug products prior to their approval.

Pediatric considerations during the NDA review of Evzio centered primarily on the safety and correct use of the auto-injector by non-medically trained individuals and the adequacy of the 0.4 mg fixed dose in providing adequate reversal of opioid effects in all pediatric patients. Given Evzio's intended use in the community setting, FDA ultimately considered the 0.4 mg auto-injector dose to be adequate for pediatric use if the product was packaged with two doses so a second dose would be available prior to the arrival of EMS. The total needle length is 5/8 of an inch, and 1/2 of an inch extends outside the device upon actuation. Due to concerns that the needle may break if bone is struck due to the needle length, a post-marketing requirement (PMR) was issued at the time of approval for a study demonstrating that the needle length was safe for use in patients less than one year of age during the expected conditions of use (PMR 2140-1).⁴³ Due to safety concerns related to auto-injector administration in small infants and children, language was added to labeling instructing caregivers to pinch the thigh of pediatric patients less than one year of age to minimize the risk of striking bone.

3. Oral Transmucosal Dosage Delivery

Oral transmucosal delivery may be an appealing route of administration in order to achieve rapid, non-invasive systemic delivery of naloxone by bypassing hepatic first pass metabolism and avoiding drug degradation in the gastrointestinal tract.⁴⁴ Naloxone formulations being developed for this route of administration must possess the physicochemical properties necessary to overcome the physiological barriers in the oral cavity without causing local irritation.

Pediatric considerations require an understanding of the physiological differences in the oral cavity between adults and children and how these differences may impact oral mucosal drug absorption. Physiological factors to consider include the following: (1) lower salivary flow rate and saliva volume in children; (2) slightly lower oral mucosal pH in children; (3) oral mucosal thickness; (4) presence of oral mucosal lesions. In addition, oral mucosal drug delivery may provoke or irritate the already damaged oral cavity in the presence of oral infections. Palatability

⁴³ April 3, 2014 Approval Letter for Evzio/NDA 205787 (accessed at Drugs@FDA August 12, 2016)

⁴⁴ Lam JKW, Xu Y, Worsley A, et al. Oral Transmucosal Drug Delivery for Pediatric Use. *Advanced Drug Delivery Reviews* 73: 50-62, 2014.

of the formulation can be a major factor determining compliance with drug delivery in pediatric patients who are awake and alert. Besides local toxicity, other safety concerns to consider may include choking risk, aspiration risk, and dosing accuracy. These local safety concerns might be acceptable given the life-threatening risk of untreated acute opioid overdose.

4. Choice of Excipients

The choice and quantity of pharmaceutical excipients must be carefully considered for formulations intended for pediatric use given the age-related developmental changes which occur with liver and renal function. Excipients generally known to be associated with increased toxicity in pediatric patients include benzyl alcohol, ethanol, and propylene glycol.⁴⁵ The need for these inactive ingredients in the specific formulation as well as data to support safe use of any inactive ingredients in pediatric patients should be provided.

5. Relative Efficacy of Different Routes of Administration

Despite the approval of IM, SC, and IN routes of administration for naloxone, product labeling states that the most rapid onset of action is achieved by IV administration. However, use of an intravenous formulation is limited to situations where trained personnel are able to obtain IV access. Pediatric use labeling for Evzio states that absorption of naloxone HCl following SC or IM administration in pediatric patients may be erratic or delayed. Similarly, pediatric use labeling for Narcan Nasal Spray contains a statement about delayed or erratic absorption in pediatric patients. This labeling also notes situations where “use of an alternate naloxone-containing product” (i.e., an intravenous formulation) would be preferred to avoid risks from abrupt opioid withdrawal. There are no well-controlled pediatric studies directly comparing the relative efficacy of the different routes of naloxone administration.

6. Utility of Multiple Approved Dosages

The utility of having multiple approved dosages of naloxone for any given formulation may depend on and should ideally be tailored to the clinical setting and on the training of the individual(s) who will be administering the dose.

Fixed doses may be more appropriate for use by lay people in community and other non-medically supervised settings where the goal would be rapid reversal of opioid effects due to acute accidental or intentional ingestion with less concern about precipitating acute withdrawal symptoms. Such settings are likely to have limited to no other treatment alternatives available.

⁴⁵ Ali AA, Charoo NA, Abdallah DB. Pediatric Drug Development: Formulation Considerations. Drug Development and Industrial Pharmacy 40 (10): 1283-1299, 2014.

Therefore, precipitation of acute withdrawal symptoms would be preferable to the potentially life-threatening consequences of prolonged respiratory depression and hypoxia due to opioid overdose.

In contrast, careful dose-titration rather than fixed dose-administration may be desirable for use by healthcare professionals in certain supervised medical settings such as post-operative recovery rooms and delivery rooms to avoid the consequences of abrupt reversal of chronic opioid effects. In addition, slower, incremental reversal of opioid effects may be justified in these settings where assisted ventilation and other supportive resuscitative measures can be provided. In opioid-dependent pediatric patients, (including neonates), administration of naloxone may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. Neonatal opioid withdrawal syndrome (NOWs), unlike opioid withdrawal syndrome in adults, may be life-threatening. In these settings, use of a naloxone-containing product that can be titrated to effect and dosed according to the infant's weight rather than as a large, fixed dose may be preferable.

Appendix A: Currently Approved Naloxone HCl Drug Products in Pediatric Patients

Product	Approval Date	Pediatric Indication	Formulation	Pediatric Dosage
Narcan NDA 016636	4/13/1971	(1) Reversal of effects of opiates with known or suspected opioid overdose; and (2) Reversal of post-operative opioid depression	Injection as sterile solution (0.02, 0.4, 1 mg/mL) IV bolus, IV infusion, SC, IM	0.01 mg/kg initial dose; If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg may be administered 0.005 mg - 0.01 mg IV at two- to three-minute intervals to desired degree of reversal; titrate dose according to patient's response. Repeat doses may be required within one- to two-hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of an opioid. Supplemental IM doses have been shown to produce a longer lasting effect
Evzio NDA 205787	4/3/2014	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression	Pre-filled auto-injector (0.4 mg/0.4 mL) IM, SC	0.4 mg initial dose; If desired response not obtained after 2 or 3 minutes, another dose may be administered. If there is still no response and additional doses are available, additional doses may be administered every 2 to 3 minutes until EMS arrive
Narcan Nasal Spray NDA 208411	11/18/2015		Pre-filled, single dose, spray (4 mg in 0.1 mL spray) IN	4 mg in 100 microliters initial dose; If desired response not obtained after 2 or 3 minutes, an additional dose should be given. If still no response and additional doses are available, additional doses should be administered every 2 to 3 minutes using a new Narcan Nasal Spray with each dose until EMS arrive

(Source: created by this reviewer from product labeling accessed at Drugs@FDA on August 8, 2016)

NDA: new drug application; CNS: central nervous system; mg: milligrams; mL: milliliters; IV: intravenous; IM: intramuscular; SC: subcutaneous; IN: intranasal; EMS: emergency medical services

Appendix B: Published Case Reports of Naloxone Use to Reverse Acute Opioid Effects in Pediatric Patients

Study	Age	Wt (kg)	Opioid Exposure	Adverse Event	Naloxone Dosing		
					Initial Dose	Route	Subsequent Doses
¹	16 months	12.5	1 Suboxone* oral tablet	Unresponsive Respiratory depression Hypotensive Miosis	Not given	Not given	Not given
¹	22 months	11	1 Suboxone* oral tablet	Somnolence Miosis	0.072 mg/kg	IV	0.5 mg/hour infusion 30 minutes later for recurrent lethargy; titrated to effect over 25 hours
¹	20 months	10	Unspecified number of Subutex [†] oral tablets	Cyanotic Somnolent Shallow respirations	0.08 mg/kg	IV	0.08 mg/kg x 1 unspecified time later for decreased heart rate
¹	15 months	12.7	1 Suboxone* oral tablet	Drowsiness	0.016 mg/kg	NOS	0.016 mg/kg x 1 unspecified time later
¹	16 months	10	1.5 Suboxone** oral tablet	Somnolent Respiratory depression Miosis	0.1 mg/kg	IV	0.1 mg/kg x 2 over 105 minutes and hours 8 and 18 post-exposure for recurrent respiratory depression
²	24 months	12.5	50 mg oral nor-methadone due to pharmacy error	Apneic CNS depression	0.008 mg/kg	IV	0.56 mg/kg total over 28 hours including 10.3 hours of infusion at 0.3 mg/hour
³	31 months	14.5	5 Tylenol # 3 oral tablets [§]	Ataxic Irritable CNS depression Respiratory depression	0.01 mg/kg	IV	0.26 mg/kg total over 9 hours 0.01 mg/kg x 1 30 minutes later for CNS depression

¹ Geib AG, Babu K, Ewald MB, et al. Adverse Effects in Children after Unintentional Buprenorphine Exposure. *Pediatrics* 118: 1746-1751, 2006.

² Gourlay GK and Coulthard K. The Role of Naloxone Infusions in the Treatment of Overdoses of Long Half-Life Narcotic Agonists: Application to Nor-Methadone. *British Journal of Clinical Pharmacology* 15: 269-272, 1983.

³ Lewis JM, Klein-Schwartz W, Benson BE, et al. Continuous Naloxone Infusion in Pediatric Narcotic Overdose. *American Journal of Diseases of Children* 138(10): 944-946, 1984.

							0.01 mg/kg IV x 2 30 minutes apart 0.027 mg/kg/hour x 2 hours and then titrated up to 0.033 mg/kg/hour for 5 hours
⁴	24 months	12.5	5 mg via Fentanyl patch transfer from grandmother	Unresponsive Choking respirations	0.04 mg/kg	IV	Re-dosed 2 hours later due to respiratory depression but dose unspecified
⁵	7 years	27	165 mg IV morphine and 65 mg IV diazepam over 1 st 2 post-operative days	Sedated Respiratory depression	0.007 mg/kg/hr	IV infusion	Infusion given for 6 days on peritoneal dialysis

*Contains 8 mg buprenorphine and 2 mg naloxone; ** Contains 2 mg buprenorphine and 0.5 mg naloxone; † Contains 8 mg buprenorphine HCl; § Exposed to 100 mg/kg acetaminophen and 10 mg/kg codeine

4 Hardwick WE, King WD, Palmisano PA. Respiratory Depression in a Child Unintentionally Exposed to Transdermal Fentanyl Patch. Southern Medical Journal 90 (9): 962-964, 1997.

5 Hasselstrom J, Berg U, Lofgren A, et al. Long Lasting respiratory Depression Induced by Morphine-6-Glucuronide? British Journal of Clinical Pharmacology 27: 515-518, 1989.



MEMORANDUM

Date: August 26, 2016

From: Gerri R. Baer, M.D.
Medical Officer/Neonatology Team Lead
Office of Pediatric Therapeutics, OPT/OSMP/OC

Through: Robert M. Nelson, M.D., Ph.D.
Deputy Director, Office of Pediatric Therapeutics, OPT/OSMP/OC

To: DAAAP/ODE II/CDER

Re: Neonatal-Perinatal Medicine Consultation: Background Information for Naloxone Advisory Committee to be held October 5, 2016

Background:

DAAAP is holding a general matters Advisory Committee meeting on October 5, 2016, for naloxone products intended for use in the community. The committee will be asked to specifically discuss the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages and the role of having multiple doses available in this setting. The committee will also be asked to discuss the criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and the labeling to inform this decision, if multiple doses are available. DAAAP has consulted DPMH and OPT Neonatology to assist in preparing for this meeting in regard to the above issues as they relate to pediatric naloxone use in this setting.

DPMH and OPT Neonatology were asked to comment specifically regarding issues related to naloxone intended for use in the community in the setting of neonatal opioid withdrawal syndrome (NOWS)/chronic in utero exposure to opioids and other scenarios where newborns may experience acute opioid toxicity, such as exposure via lactation. DPMH has provided a detailed memo covering pediatric dosing, route, and efficacy considerations as well as a summary of the information that guided approval of currently marketed naloxone products for community use.

General Neonatal Considerations for Naloxone Products Intended for Community Use:

There are two main clinical situations in which naloxone may be given to a neonate or young infant outside the medical setting. The first situation is an inadvertent acute exposure to opioid medications in an opioid-naïve neonate, either directly or via mother's milk.¹ The second is the inadvertent exposure to excess opioid in an opioid-tolerant neonate, such as a neonate with opioid withdrawal syndrome. Due to the public health crisis of opioid addiction, an increasing number of babies develop NOWS,² and some neonatal units discharge neonates and young infants home on treatment for NOWS, with a plan to taper opioids under outpatient medical supervision.

The AAP Committee on Drugs' dosing recommendations³⁻⁵ for naloxone were directed toward neonates with acute opioid exposure. Naloxone has been a mainstay of neonatal resuscitation for decades, for treatment of neonates with respiratory depression presumed secondary to known or suspected trans-placental passage of opioids. This practice is not supported by well-controlled trials with clinically meaningful endpoints,⁶⁻⁸ but in the setting of an acute opioid exposure, naloxone appears to be associated with few severe adverse events.^{9,10} There is a single case report in the literature, describing a 27 week gestation neonate who suffered asystolic cardiac arrest immediately after treatment with 0.1 mg/kg naloxone for a tenfold morphine overdose on day of life #7. The neonate was resuscitated, but expired 5 weeks later.¹¹ The widespread presence of opioid medications in U.S. households creates the potential for neonates and young infants to inadvertently receive opioids.

For neonates and infants receiving opioids to prevent NOWS, treatment with naloxone raises additional safety concerns. Reports of patients of all ages in the literature have described precipitated acute opioid withdrawal symptoms, including neonatal seizures,¹² and in non-neonatal patients, vomiting, agitation, delirium, and acute pulmonary edema when opioid-tolerant patients receive large doses of naloxone. The medical literature also contains case reports of premature atrial contractions (PACs), cardiac irritability, cardiac arrest, and sudden death in adult patients.¹⁰ An observational study from Norway described adverse events after 1192 episodes of treatment with naloxone for suspected opioid overdose. In that study (mean age 32.6 years), opioid withdrawal symptoms were described, including seizures.⁹

Neonatal Dosing and Route Considerations:

In the case of respiratory depression due to an acute exposure to opioid, the primary concern is avoiding undertreatment with naloxone. In the case of opioid toxicity in a neonate or infant receiving opioids for treatment of NOWS, there is an additional concern about precipitating acute opioid withdrawal. These competing concerns combined with the currently available evidence make it difficult to determine a single target dose for community use in neonates and young infants. Non-clinical studies and PK/PD modeling may provide information about the therapeutic window, particularly for patients with NOWS.

There are small pharmacokinetic studies describing plasma naloxone levels after intravenous or intramuscular injection.¹³⁻¹⁶ There are no data in the literature or in reviews of the currently marketed products that demonstrate predictable delivery of naloxone intranasally or subcutaneously to neonates. Obtaining these data directly would be problematic. In the outpatient setting, studies are challenging due to the infrequent use of naloxone in neonatal outpatients as well as challenges obtaining informed consent in the emergency setting. In the delivery room setting, randomization to an intranasal or subcutaneous route when IV and IM dosing are thought to be effective may create ethical challenges. Non-clinical studies may be helpful in understanding the distribution of drugs given intranasally or subcutaneously in this population.

Conclusions:

The availability of naloxone products for community use is likely to be beneficial to the neonatal population, although use in neonates will be far less prevalent than use in adolescent and adult patients who intentionally use opioids. For neonates or young infants who require reversal of effects of an acute opioid ingestion, receipt of a higher dose than required for reversal is unlikely to cause significant harm, and the primary safety concern is that of underdosing naloxone. For neonates or young infants with NOWS, who require reversal of excess opioid, the primary safety concern is avoiding the precipitation of acute opioid withdrawal syndrome. Availability of multiple doses and/or route options with clear labeling and instructions for caregivers may benefit this population.

References:

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**Department of Health and Human Services
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Office of Surveillance and Epidemiology
Drug Utilization and Epidemiology Review**

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This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

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EXECUTIVE SUMMARY

A joint meeting of the Anesthetic and Analgesic Drug Product Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) will be held on October 5, 2016 to discuss naloxone utilization in the community. In preparation for this meeting, this review provides an analysis of drug utilization patterns of naloxone in recent years, an assessment of other data resources that may capture naloxone distribution and use, and a review of the literature on naloxone distribution and use in the community.

The drug utilization analysis evaluated national estimates of naloxone sales from manufacturers to various channels of distribution between July 2011 and June 2016. Naloxone was primarily distributed to non-federal hospitals; although sales to various settings fluctuated during the study period. Sales data indicate an overall increasing trend and shift from non-federal hospitals to clinics and the outpatient retail setting. By the 12-month period ending June 2016, the market share sold to non-federal hospitals decreased to account for 53% of total naloxone sales, while clinics and retail channels increased to account for approximately 23% and 8.5% of total naloxone sales respectively. Sales to the retail channel increased for generic naloxone products, specifically 2.0mg/2ml injectable products, as well as brand Narcan Nasal Spray and Evzio auto injector, which is designed for use by non-healthcare professionals.¹ Data from U.S. outpatient retail pharmacies also show increases in the number of prescriptions dispensed for naloxone including dispensing to pediatric patients (ages 0-19 years old) during the examined time.

Much of the naloxone available for administration in acute opioid overdose rescue settings may be obtained through alternative distribution pathways that are not captured by prescription dispensing databases. Through state-level and community-based distribution programs, naloxone is commonly available to non-healthcare professionals such as police, family members, and at-risk populations (e.g. intravenous drug users and patients with substance abuse disorders). However, data on naloxone distribution and administration in these settings are generally limited; the extent to which available data characterize national naloxone usage patterns in these settings is unknown.

A search of published data found that in general, data available on naloxone use in these settings was limited to studies from Emergency Medical Services (EMS) agencies^{2,3} or take-home naloxone programs (THN) with publicly available data; again, how well these data reflect national usage is unknown. Data from THN programs are additionally limited by high participant attrition rates, unknown outcome validity, and a lack of contextual detail. Data sources identified in the literature did not assess the dose effectiveness, and effectiveness overall of naloxone administrations in these settings. Despite data showing an increasing number of multiple administrations by EMS and high proportions of reported successful opioid reversals from THN programs, the lack of contextual information on the overdose circumstances and gaps in the available information preclude a comprehensive evaluation of the appropriate dose and circumstances of naloxone administration in these settings.

1 INTRODUCTION

A joint meeting of the Anesthetic and Analgesic Drug Product Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) will be held on October 5, 2016 to discuss use of naloxone in the community. In preparation for the meeting, this review provides an analysis of drug utilization patterns of naloxone in recent years. The drug utilization data can be used as background information to provide context for the meeting discussion.

1.1 BACKGROUND

The Division of Anesthesia and Analgesic and Addiction Products (DAAAP) is evaluating naloxone hydrochloride for reversal of acute opioid overdose. The committees will be asked to discuss naloxone products intended for use in the community, specifically the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in this setting. The committees will also be asked to discuss the criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and the labeling to inform this decision, if multiple doses are available.

In this review, the Division of Epidemiology II (DEPI-II) is providing drug utilization data on the nationally estimated total number of naloxone units (generic naloxone vials/injections, units of Evzio [auto injection] and Narcan [nasal spray]) sold in the U.S. (stratified by distribution channel and product), and the nationally estimated number of prescriptions dispensed for naloxone in the outpatient retail setting stratified by patient age. Because naloxone is increasingly available in the community to non-healthcare professionals through expanded access and special distribution programs, published data on use of naloxone in the community was also evaluated. This analysis builds upon information from a previous public meeting on exploring naloxone uptake and utilization held on July 1 and 2, 2015.⁴

1.2 PRODUCT INFORMATION

Naloxone is an opioid antagonist and is thought to function by competing for mu-opioid receptors in the central nervous system displacing agonist actions from opioids and thus reversing the effects of respiratory depression and sedation.⁵ It was originally approved in 1971. Naloxone is available as an injectable formulation, auto-injector device with audible instructions, and nasal spray. Table 1 lists the currently available formulations and strengths of naloxone.

Table 1. Currently available formulations and strengths of naloxone

<u>Manufacturer/Product Name</u>	<u>Strength</u>	<u>Formulation</u>	<u>Approval date</u>
Branded Products			
Adapt® Pharma. (Narcan Nasal Spray)	4mg/spray	Nasal spray	11/18/2015
Kaleo® Pharma (EVZIO®)**	0.4mg/0.4ml	Auto-injection	04/03/2014
Generic Products			
Mylan®	0.4mg/ml 0.4mg/ml	Injection	March 6, 2014

			June 29, 2016
Hospira®	0.4mg/ml 0.4mg/ml 0.4mg/ml 0.4mg/ml	Injection	04/18/1986 01/07/1987 01/07/1987 01/07/1987
Amphastar®	0.4mg/ml 1mg/ml	Injection	01/17/1986 03/24/1988
Euro health International Sarl.	0.4mg/ml	Injection	10/22/1982

Source: Drugs@FDA.com. Accessed 08/01/2016

** Of note, the Kaleo Pharma/Evzio auto-injector is designed for use in the community by non-healthcare individuals.¹

2 METHODS AND MATERIALS

To understand the utilization of naloxone through all channels of distribution, and to gather available information on administrations in the community, several different data resources were accessed.

2.1 DRUG UTILIZATION ANALYSES

Drug utilization analyses were conducted using proprietary drug utilization databases available to the FDA. These databases included the IMS Health, IMS National Sales Perspective™ (NSP), and the IMS Health, National Prescriptions Audit™ (NPA Extended Insights). See **Appendix 3** for detailed descriptions and limitations of the databases used. The time-periods for sales analysis (July 2011 – June 2016) and prescription level data (August 2013 – July 2016) are different because of data availability of the proprietary data sources.

2.1.1 Determining Setting of Care

The IMS Health, IMS National Sales Perspective™ (NSP) database was used to determine sales of naloxone through channels of distribution to retail and non-retail settings. The **retail** setting is defined as an aggregate of sales to food stores, chain stores, and independent pharmacies. Other channels included in the analysis are non-federal hospitals, federal facilities, clinics, and a **Miscellaneous/other** (Misc.-Other) category, which includes sales to state and local governments that may supply emergency medical service providers (EMS). The **All other** category is an aggregate of Health Maintenance Organization (HMO), home health care, long-term care, mail service, miscellaneous/prisons, and miscellaneous/universities distribution channels.

2.1.2 Data Sources Used

The IMS Health, IMS National Sales Perspective™ (NSP) database was used to obtain national estimates of naloxone units (e.g. generic naloxone vials/injections, units of Evzio [auto injector] and Narcan [nasal spray]) sold from manufacturers to various channels of distribution from July 2011 to June 2016. NSP has an overall estimated sample coverage of 88% of the prescription market which is then projected to national estimates for units sold.⁶ NSP captures the number of

vials, bottles, injections, or “units” sold from the manufacturer multiplied by pack size of the unit sold. For this analysis, sales data were analyzed based on product size and strength (e.g. 2mg/2ml vial); one unit may be considered as one administration (e.g. dose of 2 mg administered) of a vial/ampule/device of naloxone.

The IMS Health, National Prescriptions Audit™ (NPA Extended Insights) was used to provide national estimates of number of dispensed prescriptions for naloxone by patient age (0-9, 10-19, 20-29, 30-39, 40-64, 65 and older) and product (e.g. 2mg/2ml vial), from outpatient retail pharmacies from August 2013 through July 2016.

Data from one Sponsor on amount of naloxone product donated in the U.S. was obtained on August 4, 2016.

2.2 COMMUNITY UTILIZATION DATABASES

2.2.1 NEMSIS Data

An abstract containing data from a recent National Emergency Medical Services Information System (NEMSIS) analysis on naloxone administration by EMS was obtained and reviewed. These analyses were led by Dr. Mark Faul of the Centers for Disease Control and Prevention (CDC), National Center for Injury Prevention and Control, in conjunction with Dr. Peter Lurie of FDA Office of the Commissioner. These data are currently being submitted for presentation at the National Association of EMS Physicians conference in 2017.

2.2.2 NPDS Data

Published annual data from the National Poison Data System (NPDS) on exposure calls taken by all poison control centers in the U.S. from 2006-2014 were aggregated and assessed. NPDS is a comprehensive poisoning exposure surveillance database in the U.S., and is maintained by the American Association of Poison Control Centers (AAPCC). NPDS contains information from human poison exposure calls taken by all poison control centers in the U.S. Case records in the database reflect information provided when the public or healthcare professionals call and report an actual or potential exposure to a substance, or request information or educational materials. Exposures do not necessarily represent a poisoning or overdose, as the AAPCC does not completely verify the accuracy of every report made to member centers. Although at the time of this review FDA did not have direct access to NPDS data, AAPCC provides aggregated national data in annual reports that are publically available online.

2.2.3 NEISS-CADES

Naloxone administrations and adverse drug events (ADEs) related to administrations were searched in the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance, or NEISS-CADES, a data resource capturing ADEs that lead to emergency department (ED) visits in a nationally representative sample of hospitals. NEISS-CADES, a joint endeavor of the Centers for Disease Control and Prevention (CDC), the Consumer Product Safety Commission, and the Food and Drug Administration (FDA), is a database that captures ADEs that result in an ED visit. Data are collected from a nationally representative sample of 63 hospitals that operate 24-hour EDs in the U.S. ADE cases are identified using clinical records where the physician explicitly links the use of a drug, or a drug-specific effect, to the condition that resulted in the ED visit. ADE outcomes collected include:

- allergic reactions

- adverse effects
- unintentional ODs
- accidental ingestions
- secondary effects, e.g. choking, or sedative effects precipitating a fall

Follow-up visits associated with prior ADEs and drugs administered in the ED are excluded. Up to 2 drugs can be recorded for each ADE. National estimates can only be reported if there are ≥ 20 cases on which to base the estimate, the coefficient of variation is $< .30$, and the estimate is $\geq 1,200$. These data were queried for ADEs involving naloxone alone (as a generic or a brand, such as Narcan or Evzio) from 2004-2014. Although these data explicitly exclude abuse-related events, NEISS-CADES data were accessed to identify ADEs associated with naloxone administration outside of an abuse setting.

2.3 LITERATURE SEARCH

A comprehensive search of literature was conducted to identify published data on community-based naloxone distribution and utilization through overdose education and naloxone distribution programs (OEND). The objective of this literature review was to summarize the recently published data on naloxone use in this setting, and its effectiveness at reversing opioid overdose.

3 RESULTS

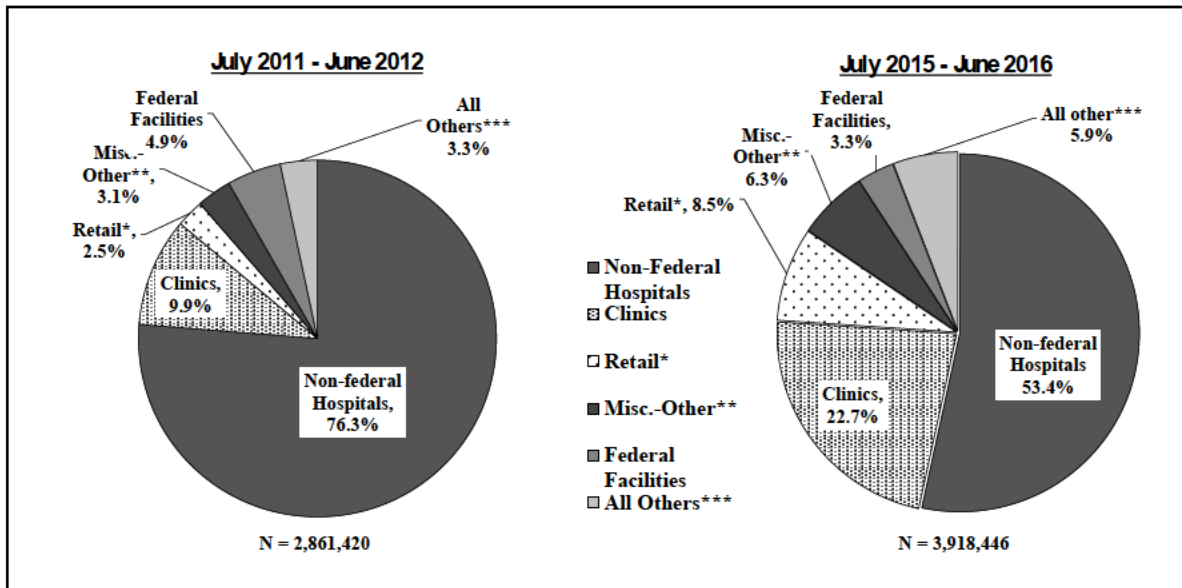
3.1 DRUG UTILIZATION ANALYSIS RESULTS

3.1.1 Sales Data

Table 4 in Appendix 1 shows the nationally estimated number of naloxone units (vials, bottles, devices) sold from the manufacturers to various channels of distribution stratified by product from July 2011 through June 2016.

Overall, the number of naloxone units sold increased by approximately 37% from approximately 2.9 million in the 12-month period ending June 2012 to 3.9 million units in the 12-month period ending June 2016 (*Figure 1*). The estimated number of naloxone units sold varied by the distribution channels. In 12-month period ending June 2012, approximately 76% of total naloxone units were sold to non-federal hospitals, 10% to clinics, 2.5% to retail, and 3% to miscellaneous-other. By the 12-month period ending June 2016, the market share sold to non-federal hospitals decreased to account for 53% of total naloxone sales while clinics and retail channels increased to account for approximately 23% and 8.5% of total naloxone sales, respectively.

Figure 1. Market share of naloxone sales by nationally estimated number of units sold from manufacturers to various channels of distribution, July 2011-June 2012 and July 2015-June 2016



Source IMS Health National Sales Perspective (NSPTM). Extracted August 2016

*Retail consists of chain stores food stores and independent pharmacies

**Misc-Other includes sales to state and local government and may supply EMS

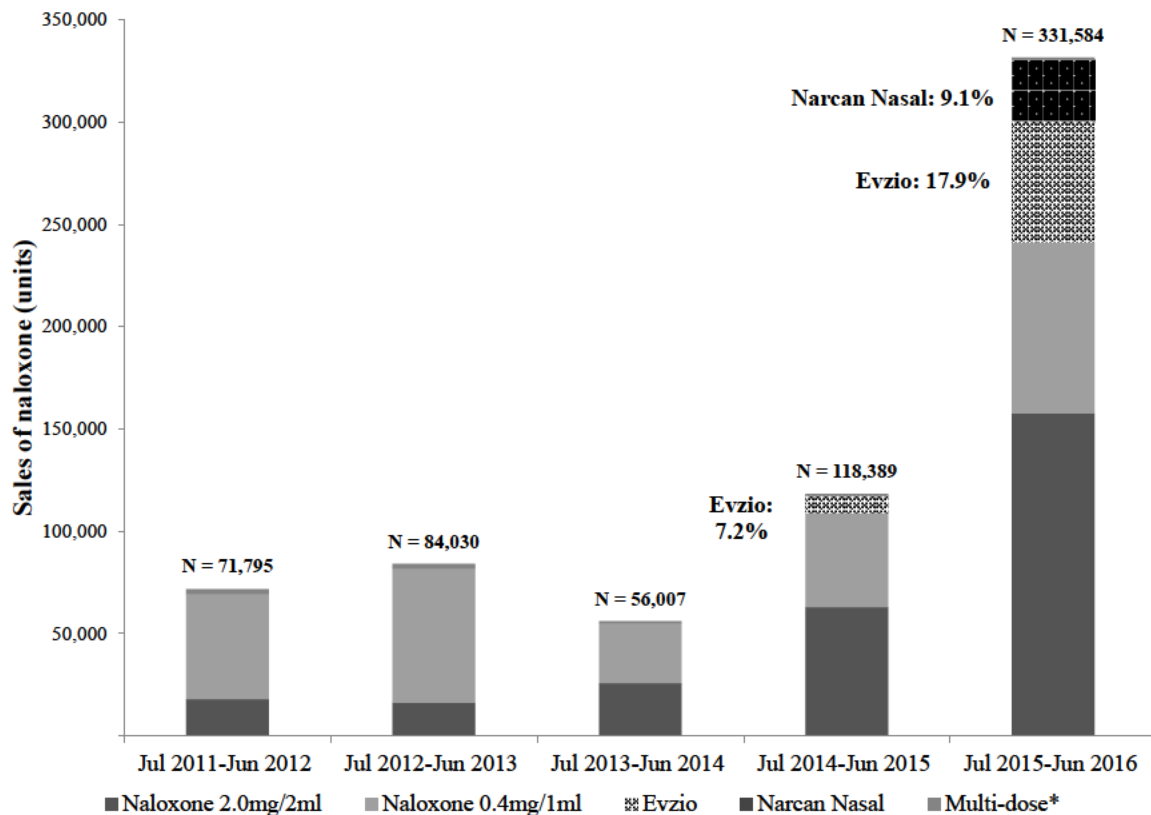
***All Other includes HMO, home health care, long-term care, mail service, miscellaneous/prisons, and miscellaneous/universities

In the 12-month period ending June 2013, approximately 76% of the units sold to non-federal hospitals were for the 0.4mg/1ml product, while in the 12-month period ending June 2016, the share for the 0.4mg/1ml product decreased to approximately 64%. During the same period, the share for the 2.0mg/2ml product increased from 21% to 33%. A similar shift in sales was observed for naloxone 0.4mg/1ml and naloxone 2.0mg/2ml in the retail channel over time.

For the miscellaneous-other channel, which includes sales to emergency medical service providers, more than twice as much 2.0mg/2ml product compared to the 0.4mg/1ml product was sold in the 12-month period ending June 2012. Sales of naloxone more than doubled within this channel and gradually shifted to be nearly evenly distributed between naloxone 0.4mg/1ml and 2.0mg/2ml at the end of the study period.

Overall, the retail channel accounted for 8.5% of total sales in the year ending June 2016. The market share for Evzio increased from 7% to 18% between June 2015 and June 2016. (*Figure 2*)

Figure 2. Nationally estimated number of naloxone units sold by manufacturers to the retail channel stratified by product strength and vial size, July 2011 to June 2016



*4mg/10ml vials

Source IMS Health National Sales Perspective (NSP™). Extracted August 2016.

3.1.2 Prescription Data by Age

Table 5 in Appendix 1 shows the nationally estimated number of prescriptions dispensed through outpatient retail pharmacies stratified by patient age for the past three 12-month periods ending in July 2016. The number of naloxone prescriptions dispensed increased from approximately 3,000 prescriptions in the 12-month period ending July 2014 to 74,000 prescriptions in the 12-month period ending July 2016. The highest proportion of naloxone prescriptions were dispensed to patients aged 40-64 years (56% of prescriptions) followed by patients aged 20-39 years (30%) and 65 years and older (13%) in the 12-month period ending July 2016. Among adults, Evzio and naloxone 2mg/2ml were the most common products dispensed.

Of the total, less than 1% of naloxone prescriptions were dispensed to pediatric patients aged 0-9 years and approximately 1% of naloxone prescriptions were dispensed to pediatric patients aged 10-19 years in the 12-month period ending July 2016. Among pediatric patients, naloxone 2mg/2ml and naloxone 0.4mg/1ml were the most common products dispensed in the 12-month period ending July 2016.

3.1.3 Naloxone Donation by the Manufacturers

Permission was received from Kaleo to disclose units of Evzio that were donated in the U.S.

between April 3, 2014 and April 3, 2015. Kaleo donated 21,130 packages (42,260 devices) of Evzio to the community. Between April 1, 2015 and April 3, 2016 Kaleo donated 60,233 packages or 120,466 devices to the community.⁷

Adapt Pharma Inc. (Narcan Nasal Spray) donated 50,000 doses of naloxone to multiple organizations.⁸

3.1.4 Summary of Drug Utilization Analysis

This analysis provides data on the nationally estimated number of naloxone products sold in the U.S. and the nationally estimated number of prescriptions dispensed for naloxone in the outpatient retail setting. Overall, the number of naloxone units sold increased by approximately 37% from approximately 2.9 million in the 12-month period ending June 2012 to 3.9 million units in the 12-month period ending June 2016. Although the majority of sales of naloxone were to non-federal hospitals, there was an increasing trend of sales to retail and clinic channels. The distribution to non-federal hospitals slightly decreased over the study period. Approximately 8.5% of naloxone sales were to the retail channel in the most recent 12-month period.

Although the majority of sales were for generic naloxone products throughout the examined time, sales of all products, both brand and generic, have increased. Narcan Nasal Spray approved in November 2015 has obtained approximately 9% of sales to the retail channel. Sales of Evzio auto-injector rapidly increased over the past two years to nearly 18% of the retail channel, possibly due to a combination of factors including increased access and availability through state and local governments, as well as a higher demand for products that can be administered by non-healthcare professionals. The increased volume of generic naloxone 2.0mg/2ml injection product sales may be attributed to demand for inclusion in naloxone kits⁹ packaged with nasal mucosal atomizers distributed through community-based naloxone distribution programs, although these nasal mucosal atomizer devices are not FDA approved.

Analyses of dispensed prescription data from U.S. outpatient retail setting indicate that the number of naloxone prescriptions dispensed increased from approximately 3,000 prescriptions in 12-month period ending July 2014 to 74,000 prescriptions in 12-month period ending July 2016. The majority of prescriptions were dispensed for naloxone 2mg/2ml injectable products and Evzio in the 12-month period ending in July 2016, although trends varied based on age.

The findings from this review should be interpreted in the context of the known limitations of the databases used. The IMS Health NSP database is a nationally representative sample of the volume of sales via the pharmaceutical supply chain, including wholesalers, capturing sales from manufacturers to various channels of distribution; the database does not capture distribution of drugs outside of the typical pharmaceutical supply chain such as donations or direct sales. Prescription level data are based on prescriptions dispensed from outpatient retail pharmacies; however, the majority of outpatient naloxone has not historically been obtained via formal outpatient prescriptions, although this appears to be increasing.

Sales of naloxone to channels of distribution assessed in these analyses may not accurately capture the volume of naloxone ultimately utilized by individuals and non-healthcare professionals. Not all naloxone sold or prescribed is ultimately used. In addition, patient-level medical chart or healthcare records are not available to validate when or who was ultimately administered naloxone. For example, it is unknown if the prescriptions dispensed for naloxone were prescribed for the intended recipient or caretaker/family member. However, these

nationally estimated data provide trends and visibility across the U.S. and may be considered a surrogate for utilization trends. Many individuals who are administered naloxone for opioid overdose during rescue situations receive these drugs from channels that are not captured through proprietary databases available to the FDA. Other resources are discussed in this review to address administrations of naloxone in specific patient populations through non-traditional distribution.

3.2 COMMUNITY UTILIZATION DATABASES RESULTS

3.2.1 NEMSIS Data

3.2.1.1 NEMSIS Results¹

Preliminary findings from an abstract of a study conducted by CDC and FDA assessed trends in multiple naloxone administrations (MNAs) from 2012-2014 submitted to NEMSIS. In 2014, EMS personnel administered naloxone 154,941 times to 127,956 patients. MNAs are increasing over time, from 14.5% of naloxone administrations in 2012 to 16.3% in 2014. Patients with the highest percentage of MNA (18.6%) were aged 20-29.

The adjusted odds ratios (aOR) for MNA versus single administrations were highest among people who live in the Northeast part of the United States (aOR=1.13, 95% CI=1.08-1.27); men (aOR=1.06, 95% CI=1.03-1.10); urban areas (aOR=1.08, 95% CI=1.01-1.14); and during the weekend (aOR=1.04, 95% CI=1.01-1.07). In terms of reason for MNA, what was referred to as “device/equipment problem” (case definition unknown) had the strongest association with MNA (aOR=15.71, 95% CI=2.71-91.0), followed by breathing problem (aOR=1.39, 95% CI=1.18-1.51). There were higher odds of MNA in reports from advanced life support (ALS) ambulances compared to basic life support (BLS) ambulances. Reported layperson naloxone administration prior to EMS arrival was rare (1%).

3.2.1.2 Summary of NEMSIS Data

The study concluded that the frequency of MNA is increasing over time, is regionally dependent, and is often associated with defective device and/or equipment and the type of ambulance service dispatched.

The National Emergency Medical Services Database, a component of the National Emergency Medical Services Information System (NEMSIS), is aggregated data submitted voluntarily by EMS agencies in more than 40 states on EMS responses to medical events. Data on the specific event responded to by the EMS, including type of medical intervention and patient disposition, are submitted by local EMS agencies, cleaned and aggregated by NEMSIS. Public use data are available from 2008 onward, and can be trended from 2010 to the present.

NEMSIS EMS data have some notable limitations. Data are voluntarily reported from a convenience sample of EMS agencies. Some data fields are free-text fields and may be missing as a result of documentation processes. Also, data are “event”-based, not “patient”-based, meaning that multiple “events” may be reported for the same underlying patient, and a single event may have multiple reports if several EMS agencies responded and recorded the circumstances surrounding this specific event.

¹ Personal Communication: Peter Lurie, FDA. July 20, 2016. Abstract submission in process.

3.2.2 NPDS Data

3.2.2.1 NPDS Results

The data in table 1 were abstracted and aggregated from published NPDS annual reports.

Table 2. Naloxone exposure call counts taken by poison control centers stratified by age, annually

Age	2006	2007	2008	2009	2010	2011	2012	2013	2014
Grand Total	13,712	15,049	16,587	17,482	18,621	19,441	19,536	19,518	20,758
< 6	621	703	892	956	1,152	1,079	1,128	1,021	1,149
6 - 12	87	87	115	105	131	132	150	162	183
13 -19	1,342	1,403	1,509	1,519	1,603	1,644	1,545	1,556	1,748
> 19	11,634	12,826	14,035	14,654	15,509	16,362	16,503	16,632	17,535
Not known	28	30	36	36	28	30	19	16	22

Extracted from AAPCC annual reports

3.2.2.2 Summary of NPDS Data

From 2006 through 2014, the total naloxone administrations captured by poison control centers increased every year from 13,712 in 2006 to 20,758 in 2014, representing a 51% increase. The vast majority of these administrations were given to those over 19 y/o. It is unclear from these data who administered the naloxone and whether it was effective.

For this evaluation, DEPI reviewed the annual reports from 2006 through 2014 for mentions of naloxone.¹⁰⁻¹⁸ These naloxone mentions represent administrations of naloxone given by health professionals or lay-persons that were ultimately reported to poison control. Because these data are passively collected, these numbers likely reflect an underestimate of community administrations.

3.2.3 NEISS-CADES Data

3.2.3.1 NEISS-CADES Results

There were not enough cases (ADE outcomes listed above) involving naloxone alone (not in combination products with an opioid for medication assisted treatment) to produce reliable national estimates therefore these data are not reported.

3.3 OBSERVATIONAL STUDY LITERATURE RESULTS

This literature search was conducted using PubMed, and was restricted to only published, U.S.-based observational studies and randomized controlled studies from the last 10 years with a specific focus on naloxone use by non-healthcare individuals in the community.

The literature search identified over 1200 articles, but the vast majority were not relevant to the study questions. Two systematic reviews were identified and articles referenced in the reviews were also evaluated. The studies described below represent only the most relevant studies identified in this search.

Systematic review: MacDonald 2016 and Clark 2014^{19,20}

Two recently published systematic reviews, McDonald (2016) and Clark (2014), aimed at assessing the effectiveness of take home naloxone (THN) programs, were reviewed. Both the McDonald and Clark systematic reviews had similar methodologies for identifying and aggregating germane studies. Standard electronic article reference databases (PubMed, Embase, Medline, etc.) were searched for any study related to community naloxone distribution programs (U.S. and otherwise) with data on naloxone use and outcomes (overdose reversals, etc). Because the search criteria for both reviews were largely the same, many of the studies that were included in McDonald (n=22) and Clark (n=19) overlap. The table of included studies for McDonald, with data on how many THN kits were distributed and ultimately used during an overdose, as well as information on overdose reversals, is presented below (Table 3) A table of studies included in Clark is in **Appendix 2**. In general, there was substantial variability in how many THN kits were distributed and the percentage subsequently used (0.5%-67%) based on the program studied; however, nearly all studies reported 100% or nearly 100% (lowest 83%) opioid overdose reversals after THN administration. Both McDonald and Clark found that the most common drug reported to have precipitated the overdose was heroin.

Table 3. Characteristics of studies in systematic review by MacDonald 2016

Table 3 Included studies: naloxone kits distributed and used, overdose reversals and adverse events.

Study	n	THN kits distributed	THN kits used (%)	Deaths	OD reversal after THN ^e	Unknown outcomes	Adverse reactions
Bennett 2011	426	426	249 (58%)	2	≥ 96%	8	NR
Bennet 2012	525	NR	28 (NR)	1	96%		NR
Dettmer 2001 ^f	101	101	5 (5%)	0	100%		Withdrawal (NR)
Dettmer 2001 ^f	124	124	29 (23%)	0	100%		Withdrawal (10)
Doe-Simkins 2009 ^d	385	385	74 (19%)	0	100%		Withdrawal (2)
Dwyer 2015 ^d	415	56	6 (11%)	0	100%		NR
Enteen 2010	1942	2962	399 (13%)	6	≥ 89%	36	Vomiting (50), agitation (36), seizures (3)
Galea 2006	25	25	10 (40%)	1 ^a	100%	1 ^a	None
Lankenau 2013 ^d	30	30	15 (50%)	0	≥ 97%	1	NR
Leece 2013	209	209	17 (8%)	0	100%		None
Lopez-Gaston 2009	70	70	0 (0%)	1 ^a	NA		NA
Markham Piper 2008	122	122	82 (67%)	0	≥ 83%	14	NR
Maxwell 2006	1120	3500	319 (9%)	1 ^c	99%		Seizures (1), vomiting (1)
McAuley 2010	41	19	2 (11%)	1 ^a	100%		NR
Rowe 2015	2500	2500	702 (28%)	10	99%		NR
Seal 2005	24	24	15 (63%)	0	100%		NR
Strang 2008	239	239	1 (5%)	1 ^a	100%		Withdrawal
Tobin 2009	250	250	22 (9%)	0	100%		NR
Tzemis 2014	692	836	85 (10%)	0	100%		Withdrawal (55), agitation (9)
Wagner 2009	66	66	28 (42%)	4 ^b	NR	5	Agitation (5), vomiting (1)
Walley 2013 [20]	2912	2912	327 (11%)	0	100%		NR
Walley 2013 [33] ^d	1553	1553	92 (6%)	0	100%		NR
Yokell 2011	120	120	5 (4%)	0	100%		NR

^aNaloxone not administered; ^bunclear if naloxone administered; ^cnon-opioids present; NA: not applicable; NR: not reported; OD = overdose; THN: take-home naloxone; ^dnot included in summary measures to avoid (partial) duplication of samples; ^ewhere applicable, unknown outcomes were counted towards unsuccessful THN administrations (as indicated by the ≥ symbol); ^fMulti-site study with two samples: Jersey (n=101) and Berlin (n=124).

To investigate whether additional useful data were presented in the studies that were included in both reviews, studies based in the United States and published in the last 10 years were independently reviewed. Most of the studies did not contain any additional information as it relates to the Agency's specific questions of interest regarding naloxone. Of the ones that did, Doe-Simkins et al (2009)²¹, using a Boston-based cohort of 385 trained participants or "potential bystanders" given THN between 2006-2007 found that of the 278 that were followed-up with, two of the "potential bystanders" (those given THN) reported that naloxone "wore off" after it was administered. In one case it was re-administered by the "bystander"; in the other case the affected person remained sedated until EMS could come to assist.

Consistent with the review's finding that most THN kit use was associated with heroin overdose, Rowe et al (2015)²², using a San Francisco-based cohort of the 702 reported reversals between 2010-2013, found that of the substances reported to have precipitated the overdose, heroin was reported in 634 cases (90.3%). In 379 cases (54.0%), heroin was the only drug reported, and in 255 cases (36.3%) heroin was reported with "other substances". In a Baltimore based cohort of 43 trained participants between 2004-2005, Tobin et al (2009)²³ found that of the 19 individuals that used injectable naloxone, 14 reported only 1 injection, 4 reported 2 injections, and 1 reported 3 or more injections at the last overdose they witnessed and/or assisted on. In a Massachusetts-based cohort of 327 trained enrollees from 19 communities between 2006 -2009, Walley et al (2013)²⁴ found that of the 312 individuals that reported rescue attempts and recorded how many doses were used, 48% reported using 1 dose, 48% reported using 2 doses, and 4% reported 3 or more doses.

Knowlton 2013 Baltimore²:

In a study by Knowlton et al (2013), data from the Baltimore City Fire Department EMS patient records were matched to dispatch records from 2008-2009. There were 116,910 EMS incidents for patients ≥ 15 y/o over the study period, and naloxone was administered during 1,297 (1.1%) of those incidents. Intranasal naloxone was administered most frequently (40%), followed by intravenous (27%), and intramuscular (22%). Mean naloxone dosage administered was 1.3 mg (range 0.02-2.4 mg). Patient status immediately following naloxone administration was recorded in 85% of incidents (n=1,102). Of the recorded status after administration, in 62% the patient improved (n=804), in 23% there was no change (n=298), in 0.2% the patient worsened (n=26), and for 0.4% the patient change could not be assessed (n=52). Ninety-one percent of incidents in the analysis (n=1,180) involved ED transport for further care.

Wheeler 2015²⁵:

Wheeler et al with the Harm Reduction Coalition and the Opioid Safety and Naloxone Network conducted a survey of 136 managers of naloxone distribution programs excluding law enforcement and medical personnel in 2014. There were 84 community based organizations, 18 health care facilities, 10 VA facilities, 18 state and local health departments, and 6 pharmacies involved in the survey totaling 644 local opioid overdose prevention sites. From 1996 to 2014 a total of 152,283 kits were provided to individuals and lay-persons, and 26,463 documented reversals submitted by 109 sites.

In 2013, 37,920 people received naloxone from 93 organizations and there were a total of 8,032 reversals. Approximately 50% of the overdose prevention sites provided naloxone in an injectable formulation and over one-third provided naloxone packaged in a kit with a nasal mucosal atomizer; more than 10% provided naloxone in both formulations. Eleven of the largest organizations provided over 75% of the naloxone distributed through these community distribution programs during the study period.

Greene 2015 Massachusetts and Rhode Island²⁶:

In March 2014, Massachusetts implemented a standing order policy for naloxone with the medical director of the state health department serving as the sole prescriber for the state. In July 2014, a state-wide standing order law was enacted. Pharmacists were permitted to dispense naloxone to patients perceived to be at risk of opioid overdose. In Rhode Island, there was a surge in overdose deaths attributed to fentanyl. In response to this increase in overdose mortality, pharmacists and prescribers initiated a collaborative practice agreement among select pharmacies, and Rhode Island doubled the community based distribution of naloxone. Between January 2014 and May 2015, 572 prescriptions, or 25% of all naloxone distributed, were dispensed via these collaborative practice agreements.

Piper 2008 New York City²⁷:

In a cross-sectional study to examine rescue naloxone use by intravenous drug users (IDUs) from March to December 2005, Piper evaluated a collaborative program between the New York City Syringe Exchange Program and the Harm Reduction Coalition. This program was modeled after both the Chicago Recovery Alliance and Drug Overdose Prevention and Education (DOPE) from San Francisco. A large proportion of program participants were male (87%), and over half were homeless in the prior 6 months. Over 70% were also involved in a methadone treatment program. Participants were initially interviewed and trained on rescue naloxone use. They were given one kit with two 1mg/1ml doses of naloxone, and filled out a 33-item questionnaire when they returned to request additional kits. Of 122 enrolled, 71 witnessed an overdose and 50 used naloxone. Eighty-two doses were administered and 68 overdose victims survived. Although information was mostly self-reported, heroin was documented to be involved in 88% of overdoses.

Wagner 2010 Los Angeles²⁸:

Wagner et al evaluated a 1-hour training program on supportive care for overdose victims that included rescue naloxone use in a Los Angeles community-based intravenous drug use program called, the Homeless Health Care Los Angeles Center for Harm Reduction. This program was modeled after the approach from the Chicago Recovery Alliance. After training on rescue naloxone use, participants met with a physician, and a naloxone rescue kit was provided with a 4mg/1ml naloxone dose. Prior naloxone use was self-reported by participants when requesting refills of the naloxone kit. Ninety-three participants completed the training, and 47 participants completed both a pre and post training interview. Seventy-three percent of participants who completed opioid overdose training were homeless. During the follow-up period between September 2006 and January 2008, 22 participants were involved in 35 rescue situations. Twenty-six overdose victims recovered, while 4 died. Ninety-seven percent reported the use of heroin as the drug precipitating the overdose.

Walley 2013 Boston²⁹:

In 2007, Massachusetts developed an opioid overdose prevention pilot program across several agencies. Walley et al describes characteristics of the overdose education and naloxone distribution (OEND) program, specifically for those taking methadone in substance abuse and HIV prevention programs. Enrollment occurred between September 2008 and December 2010 and included those with any methadone use during the previous 30 days. A total of 1553 participants were included in the sample. Settings of care were methadone maintenance treatment programs, supervised withdrawal programs, detox programs, HIV prevention programs, and other healthcare and non-healthcare settings. The OEND program was modeled after other Chicago Recovery Alliance associated programs. Naloxone rescue kits consisted of two 2mg/2ml pre-filled syringes packaged with two mucosal atomizers. A questionnaire at enrollment documented

demographics and history of overdose. An additional questionnaire was completed during the refill encounter that included characteristics of naloxone use for rescue. Almost 50% of participants were enrolled in detox programs and 35% were enrolled in HIV prevention programs. 17% were in methadone maintenance treatment program (MMTP) methadone clinics. There were a total of 92 overdose rescues, 23 in the detox group and 53 in the HIV prevention group. Heroin was involved in more than 90% of the overdoses, and methadone was reported being involved in 4.8% of overdoses.

Harm Reduction Coalition⁹:

The Harm Reduction Coalition (HRC), founded in 1993, is a national organization working with needle exchange programs and public health advocacy groups focused on patients with substance abuse disorders. The HRC Manual provides instructions on naloxone rescue kit assembly and appropriate administration of naloxone for rescue situations, including the use of an atomizer. In 2010, the HRC conducted an initial survey to characterize community-based distribution programs. They state over 53,032 were trained and given naloxone as part of overdose education and naloxone distribution programs from 48 states and 188 sites. The HRC documented a total of 10,071 overdose reversals. Below are brief descriptions of major collaborators in the Harm Reduction Coalition initiatives for rescue naloxone use.

Chicago Recovery Alliance (Chicago, IL):

In 2010, the Chicago Recovery Alliance (CRA) helped enact “Good Samaritan” laws that protect those involved in rescue of overdose victims such as laypersons and prescribers of naloxone from any liability associated with possessing naloxone without a prescription and administering naloxone on individuals presumed to be overdosing. The CRA also developed the “SCAREME” tactic which stands for Stimulation, Call 911, Rescue Breathing, Evaluate the Situation, Muscular Injection, Evaluate. The SCAREME approach became a model for other THN and OEND initiatives. Between 2001 and 2011 the CRA has provided 22,010 overdose prevention encounters, and received reports of 2,720 opioid overdose reversals. Naloxone is provided to participants after appropriate training free of charge and outside of a pharmacy by trained non-medical staff.

Clean Works program (Grand Rapids MI):

In October 2008, the Clean Works Program in Grand Rapids Michigan partnered with local physicians to provide naloxone in an existing syringe exchange program. The program began using the SCAREME protocol developed by the Chicago Recovery Alliance. The program states that through August 2011 they have provided 209 trainings and received reports of 64 overdose reversals. The program also states that in 2010 overdose fatalities stabilized and started decreasing in Kent County.

Project Lazarus (Wilkes County NC):

Project Lazarus uses a physician to identify at -risk patients and helps to coordinate naloxone distribution with select pharmacies that provide free rescue kits. During this program overdose death rates in the region dropped 42% from 2009 to 2010. Emergency department visits related to substance abuse dropped by 15.3% from 2008 to 2010. In 2010 10% of fatal overdoses were related to prescription opioids compared to 82% in 2008.

Not One More Anonymous Death (NOMAD):

NOMAD is a statewide comprehensive naloxone distribution program in Massachusetts that began in late 1990s. In a collaboration between the Massachusetts Department of Public Health, Office of HIV/AIDS, and Bureau of Substance Abuse Services, the

program trained over 10,000 individuals and received reports of 1,200 overdose reversals. The Massachusetts Department of Public Health provides nasal naloxone, mucosal atomizer, and educational materials to approved agencies for distribution.

4 DISCUSSION

Nationally estimated sales of naloxone from manufacturers to various channels of distribution provide information on trends and general characteristics of naloxone availability across the U.S. Over the five years examined, sales distribution of naloxone across all settings of care increased by approximately 37% to a total of 3.9 million naloxone units sold in the 12-month period ending June 2016. Although the majority of sales were to non-federal hospitals, market share of naloxone sales distributed to retail and clinic settings have increased.

Over a three year period, the nationally estimated number of naloxone prescriptions dispensed from outpatient retail pharmacies increased exponentially from approximately 3,000 prescriptions dispensed in the 12-month period ending in July 2014 to 74,000 prescriptions in the 12-month period ending in July 2016. In addition to increases for generic naloxone products, both dispensed prescription data and sales distribution data trends show market uptake for the two most recently approved products, Narcan Nasal Spray and Evzio auto-injector since approval. In terms of patient demographics, approximately 2% of total naloxone prescriptions were dispensed to pediatric patients 0-19 years old in the 12-month period ending July 2016.

Due to the indication for naloxone, some naloxone prescriptions may be unique in that the “patient” and the corresponding patient demographics indicated on the dispensed prescription may or may not be the intended recipient of the naloxone. Prescriptions may have been prescribed to family members or caretakers of patients who may encounter an overdose situation, although this cannot be confirmed due to our lack of access for medical chart validation.

Many of the individuals most likely to administer naloxone in a rescue situation may not have obtained the drug from a formal prescription dispensed from a pharmacy. At both the state and local levels, new policies are being adopted to expand access to naloxone by implementing state-wide standing orders, collaborative practice agreements, and distribution to first responders.³⁰ The quantity of naloxone that may be distributed to community-based programs from these traditional channels is not known. Some patients may not have financial resources or healthcare coverage to obtain naloxone even if mechanisms such as state standing orders are in place. Police and EMS personnel frequently use naloxone to revive victims of suspected overdose; the products used in this situation are not prescribed and would not be obtained from a pharmacy.⁹

Currently, more than 25 states have enacted some form of legislation to expand access to naloxone, and a proportion of naloxone is administered through these non-traditional channels without prescriptions.³² In December 2015, HHS proposed a budget to SAMHSA that included 12 million dollars in funding to states to purchase and distribute naloxone for overdose prevention. Depending on how the product is obtained, naloxone distributed outside of traditional prescription dispensing channels may not be included in pharmaceutical sales data; this would result in an underestimate of the amount of naloxone distributed in the U.S. Unfortunately, national level data on naloxone distribution and administration through non-traditional channels are limited, and systems are not yet in place that can adequately characterize the prevalence and frequency of community-based naloxone use by lay-persons or first-responders.

In general, published data on naloxone use in these settings are restricted to EMS data (NEMSIS, and Knowlton, 2013), or take-home naloxone (THN) programs, and it is unknown what proportion of naloxone use this represents. Although, data from EMS may be the most comprehensive, these data are submitted voluntarily, and their ability to accurately estimate naloxone use by first responders nationally is unknown. Data from THN programs are lacking detail, and are limited by high participant attrition rates, unknown outcome validity, and the lack of detail regarding the specific circumstances that surround the overdose event, such as the condition of the affected person before and/or after administration. Inferences cannot be made about the total amount of naloxone distributed from all THN programs based on what is publicly available as there may be many more programs that distribute naloxone that do not publish their data.²⁵

Similarly, in regard to the effectiveness of naloxone in the community, no definitive conclusions can be made based on the data provided given their limitations. Despite data showing an increasing number of multiple administrations by EMS (NEMSIS data), and high proportions of reported successful opioid reversals^{19,20} it would not be appropriate to evaluate effectiveness based on a small amount of data that lack context and validation. For instance, although multiple naloxone administrations by EMS may be increasing, it is not clear whether this is due to increased potency in the drug consumed by the affected person, error related to the naloxone administration, or other clinical details related to the rescue attempt. The epidemiological data on naloxone use outside of traditional channels do suggest that heroin precipitates a majority of the overdoses when naloxone is used.

Additional data are needed on the amount of naloxone distributed from all channels of distribution, including the community-based and state-financed naloxone programs. Additional information is also needed about the circumstances surrounding the emergency response, including whether multiple doses were used, what formulation and dose was used, whether it was effective at reversing the overdose, and what specific opioid caused the overdose being treated.

5 CONCLUSION

This drug utilization review is focused on trends in use of naloxone for opioid overdose rescue administration in the U.S. Data are presented from proprietary drug utilization and community databases, as well as the published literature.

Over a five year period, the number of naloxone units sold nationally from manufacturers increased by approximately 37% over a five year period to a total of 3.9 million units sold in the 12-month period ending June 2016. Distribution of generic naloxone products as well as Narcan and Evzio increased in terms of both sales to retail and clinic channels as well as outpatient retail prescriptions over the examined time. Based on U.S. outpatient retail dispensed prescription data, pediatric patients (ages 0-19 years old) were also dispensed prescriptions for naloxone in the outpatient setting.

In regards to the distribution of naloxone from the community based programs outside of traditional channels, published data are limited and difficult to interpret. State and local communities are increasingly adopting policies to expand access to naloxone using a variety of initiatives and programs, and it is unknown what proportion of naloxone this represents out of the universe of naloxone distributed.

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APPENDICES

APPENDIX 1: TABLES AND FIGURES

Table 4. Nationally estimated number of naloxone products (in units) sold from manufacturers to channels of distribution from July 2011 to June 2016

Channel	Jul 2011-Jun 2012	Share %	Jul 2012-Jun 2013	Share %	Jul 2013-Jun 2014	Share %	Jul 2014-Jun 2015	Share %	Jul 2015-Jun 2016	Share %
Grand Total	2,861,420	100%	3,203,536	100%	2,575,198	100%	3,232,282	100%	3,918,446	100%
Non-Federal Hospitals	2,182,164	76.3%	2,227,034	69.5%	1,654,959	64.3%	1,870,597	57.9%	2,092,609	53.4%
Naloxone (0.4mg/1ml) Inj	1,411,416	64.7%	1,687,012	75.8%	1,108,135	67.0%	1,223,930	65.4%	1,344,697	64.3%
Naloxone (2.0mg/2ml) Inj	603,382	27.7%	472,005	21.2%	495,358	29.9%	577,361	30.9%	692,055	33.1%
Multi-dose (4mg/10ml) Inj	167,366	7.7%	68,017	3.1%	51,466	3.1%	69,280	3.7%	46,855	2.2%
Narcan Nasal									8,886	0.4%
Evzio							26	0.0%	116	0.0%
Clinics	282,134	9.9%	393,309	12.3%	552,061	21.4%	725,404	22.4%	887,926	22.7%
Naloxone (0.4mg/1ml) Inj	201,164	71.3%	315,691	80.3%	371,304	67.3%	501,523	69.1%	597,291	67.3%
Naloxone (2.0mg/2ml) Inj	59,244	21.0%	67,881	17.3%	159,180	28.8%	198,195	27.3%	263,931	29.7%
Multi-dose (4mg/10ml) Inj	21,726	7.7%	9,737	2.5%	21,577	3.9%	25,522	3.5%	21,126	2.4%
Narcan Nasal									4,408	0.5%
Evzio							164	0.0%	1,170	0.1%
Retail	71,795	2.5%	84,030	2.6%	56,007	2.2%	118,389	3.7%	331,584	8.5%
Naloxone (2.0mg/2ml) Inj	17,831	24.8%	16,244	19.3%	25,853	46.2%	62,873	53.1%	157,662	47.6%
Naloxone (0.4mg/1ml) Inj	51,234	71.4%	65,512	78.0%	29,185	52.1%	45,986	38.8%	83,339	25.1%
Evzio							8,538	7.2%	59,246	17.9%
Narcan Nasal									30,174	9.1%
Multi-dose (4mg/10ml) Inj	2,730	3.8%	2,274	2.7%	969	1.7%	992	0.8%	1,163	0.4%
Misc.-Other*	89,451	3.1%	206,660	6.5%	119,276	4.6%	264,154	8.2%	246,946	6.3%
Naloxone (2.0mg/2ml) Inj	60,535	67.7%	69,661	33.7%	78,971	66.2%	109,732	41.5%	127,400	51.6%
Naloxone (0.4mg/1ml) Inj	19,124	21.4%	116,955	56.6%	32,136	26.9%	142,463	53.9%	109,946	44.5%
Multi-dose (4mg/10ml) Inj	9,792	11.0%	20,044	9.7%	8,169	6.9%	11,957	4.5%	8,632	3.5%
Narcan Nasal									954	0.4%
Evzio							2	0.0%	14	0.0%
Federal Facilities	140,215	4.9%	125,679	3.9%	83,150	3.2%	120,497	3.7%	130,343	3.3%
Naloxone (0.4mg/1ml) Inj	74,335	53.0%	92,249	73.4%	47,047	56.6%	66,518	55.2%	71,878	55.2%
Naloxone (2.0mg/2ml) Inj	54,696	39.0%	27,328	21.7%	31,448	37.8%	49,642	41.2%	53,690	41.2%
Multi-dose (4mg/10ml) Inj	11,184	8.0%	6,102	4.9%	4,655	5.6%	4,189	3.5%	2,967	2.3%
Evzio							148	0.1%	1,106	0.9%
Narcan Nasal									702	0.5%
All other**	95,661	3.3%	166,824	5.2%	109,745	4.3%	133,241	4.1%	229,038	5.9%
Naloxone (0.4mg/1ml) Inj	67,205	70.3%	140,794	84.4%	85,933	78.3%	99,664	74.8%	162,889	71.1%
Naloxone (2.0mg/2ml) Inj	16,370	17.1%	20,424	12.2%	21,328	19.4%	30,655	23.0%	53,646	23.4%
Evzio							396	0.3%	6,046	2.6%
Narcan Nasal									4,116	1.8%
Multi-dose (4mg/10ml) Inj	12,086	12.6%	5,606	3.4%	2,484	2.3%	2,526	1.9%	2,341	1.0%

*Misc-Other includes sales to state and local government and may supply Emergency Medical Services (EMS)

**All Other includes HMO, home health care, long-term care, mail service, miscellaneous/prisons, and miscellaneous/universities

Source IMS Health: National Sales Perspective (NSP™). Extracted August 2016.

Table 5. Nationally estimated number of naloxone prescriptions dispensed in the outpatient retail setting stratified by product and patient age from August 2013 to July 2016

Age	Aug 2013 - Jul 2014	Share %	Aug 2014 - Jul 2015	Share %	Aug 2015 - Jul 2016	Share %
Grand Total	3,031	100%	13,360	100%	74,123	100%
0-9 years old	91	3.0%	252	1.9%	428	0.6%
Naloxone (2.0mg/2ml) Inj	34	37.4%	152	60.3%	253	59.1%
Naloxone (0.4mg/1ml) Inj	57	62.6%	100	39.7%	129	30.1%
Narcan nasal					42	9.8%
Evzio					4	0.9%
10-19 years old	171	5.6%	276	2.1%	818	1.1%
Naloxone (2.0mg/2ml) Inj	64	37.4%	99	35.9%	337	41.2%
Naloxone (0.4mg/1ml) Inj	100	58.5%	149	54.0%	204	24.9%
Evzio			24	8.7%	187	22.9%
Narcan nasal					89	10.9%
Multi-dose (4mg/10ml) Inj*	3	1.8%	3	1.1%	1	0.1%
Unspecified Product**	4	2.3%	1	0.4%		
20-39 years old	792	26.1%	3,857	28.9%	21,924	29.6%
Naloxone (2.0mg/2ml) Inj	506	63.9%	2,532	65.7%	8,568	39.1%
Evzio	17	2.2%	801	20.8%	8,420	38.4%
Narcan nasal					3,273	14.9%
Naloxone (0.4mg/1ml) Inj	251	31.7%	512	13.3%	1,660	7.6%
Multi-dose (4mg/10ml) Inj*	4	0.5%	4	0.1%	2	0.0%
Unspecified Product**	14	1.8%	8	0.2%	1	0.0%
40-64 years old	1,435	47.3%	7,058	52.8%	41,276	55.7%
Evzio	59	4.1%	2,962	42.0%	19,061	46.2%
Naloxone (2.0mg/2ml) Inj	908	63.3%	3,103	44.0%	11,577	28.1%
Narcan nasal					7,575	18.4%
Naloxone (0.4mg/1ml) Inj	391	27.3%	937	13.3%	2,990	7.2%
Multi-dose (4mg/10ml) Inj*	2	0.1%	6	0.1%	23	0.1%
Unspecified Product**	75	5.2%	50	0.7%	50	0.1%
65 years old and over	394	13.0%	1,748	13.1%	9,582	12.9%
Evzio	20	5.1%	700	40.1%	3,702	38.6%
Naloxone (2.0mg/2ml) Inj	173	43.9%	693	39.7%	2,855	29.8%
Narcan nasal					2,067	21.6%
Naloxone (0.4mg/1ml) Inj	180	45.7%	326	18.7%	936	9.8%
Multi-dose (4mg/10ml) Inj*			3	0.2%	10	0.1%
Unspecified Product**	21	5.3%	26	1.5%	12	0.1%
Unspecified Age	148	4.9%	169	1.3%	95	0.1%

Source IMS Health: National Prescription Audit Extended (NPA Extended™). Extracted August 2016.

APPENDIX 2: SYSTEMATIC REVIEW TABLES

Table 6. Table of included studies in Clark 2014

Authors (Year)	Program Name	Program Site (Location)	Sample Size	Time Frame	Outcomes			Training Content (Duration/Setting)
					Num Nal Admin/Num Indiv Used Nal/Num Witnessed Overdoses	% Survived After Nal/Change in Knowledge	% Follow Up/ Sources of Outcome Data	
Bennett et al. (2011)	Prevention Point Pittsburg	Syringe exchange program (Pittsburgh, Pennsylvania)	425	July 2005–December 2008	249/89/NR	96%/NR	33%/ nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Needle-based nal admin (25 min/provided by staff or volunteers)
Bennett and Holloway (2012)	Take Home Naloxone Demonstration Project	Multiple sites including community settings and prison sites (Wales)	525	September 2009–September 2010	28/NR/NR	96%/ Stat sig increased knowledge of risk factors; Confidence with nal admin increased from 67% to 92%; Mouth to mouth resuscitation increased from 69% to 88%	5%/pre- and posttraining and nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS CPR Needle-based nal admin First aid (1 hr/group with 1-3 trainers)
Dettmer et al. (2001)	NR	Mobile services for drug users (Berlin, Germany) and local drug service locations (Jersey, United Kingdom)	Berlin = 124; Jersey = 101	January 1999–April 2000; October 1998–February 2000	Berlin: 29/22/NR; Jersey: 5/NR/NR	100% in both locations/NR	33% (Berlin) and NR (Jersey)/ spontaneous self-report (Berlin) and NR (Jersey)	Emergency resuscitation Needle-based nal admin (NR)
Doe-Simkins et al. (2009)	Boston Public Health Commission Naloxone Distribution Program	Syringe exchange program (Boston, Massachusetts)	385	September 2006–December 2007	74/50/NR	100%/NR	72%/nal refill form	Overdose prevention Intranasal nal admin (15 min/NR)
Esteen et al. (2010)	Drug Overdose Prevention and Education Project	Syringe exchange programs, reentry programs, opioid substitution clinics, pain management clinics, and single room occupancy hotels (San Francisco, California)	1942	September 2003–December 2009	399/310/NR	89%/75% of participants who used nal also used complementary overdose prevention strategies	24%/nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Nal admin Mechanism of overdose Aftercare (10-30 min/NR)
Galea et al. (2006)	Overdose Prevention and Reversal Program	Syringe exchange program (New York, New York)	25	June 2004–January 2005	10/NR/26	100%/increase for 58% to 82% of respondents called ambulance for last witnessed overdose at FU	88%/baseline and 3-mo FU survey	Recognize overdose Activate EMS Rescue breathing Needle-based nal admin (1 hr/small group or indiv plus indiv meeting with physician)

(Continues)

TABLE 2. Articles Included in Review (Continued)

Authors (Year)	Program Name	Program Site (Location)	Sample Size	Time Frame	Outcomes			
					Num Nal Admin/Num Indiv Used Nal/Num Witnessed Overdoses	% Survived After Nal/Change in Knowledge	% Follow Up/Sources of Outcome Data	Training Content (Duration/Setting)
Lopez Gaston et al (2009)*	NR	Detox center and community drug treatment teams (Birmingham and London, England)	70	January 2006-January 2007	0/NR/16	NA/stat sig mean increase from baseline to 6 mo FU in knowledge of overdose signs and in knowledge of actions to take in an overdose event	82.8% at 3 mo and 65% at 6 mo/pre- and posttraining survey and FU surveys at 3 and 6 mo	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Recovery position Needle-based nal admin (30 min/group of 3-10 or indiv)
Lankenau et al (2013)	Homeless Healthcare Los Angeles and Common Ground Westside	Community health care programs, including syringe exchange (Los Angeles, California)	30	2010-2011	15/NR/30	100%/NR	NA/interview containing closed- and open-ended questions	Recognize overdose Activate EMS Rescue breathing CPR Needle-based nal admin (NR/NR)
Leece et al (2013)	Prevent Overdose in Toronto	Syringe exchange program and partner sites (Toronto, Ontario)	209	August 2011 - April 2012	17/NR/NR	100%/NR	NR/spontaneous self-report	Overdose prevention Recognize overdose Activate EMS Chest compressions Needle-based nal admin Aftercare Nal kit care and logistics (20 min/indiv or small group by RN or counselor)
Maxwell et al (2006)	Chicago Recovery Alliance	Multiple sites targeting active injection drug users (Chicago, Illinois)	NR (approx 3500 multidose vials of naloxone provided)	January 2001-NR	319/NR/NR	99%/anecdotal reports of increased self-efficacy and personal concern for health after being involved in OOPP	NR/spontaneous self-report	Pharmacology of opioids and nal Opioid neurophysiology Overdose prevention Risk factors for overdose Recognize overdose Rescue breathing Prevention of choking and aspiration Needle-based nal admin Aftercare (NR/NR)
McAuley et al (2010)	Lanarkshire Naloxone Pilot	Ambulance service users (Scotland)	19	NR	2/NR/3	100%/knowledge scores improved from mean of 7.03 at baseline (n = 33) to 10.54 at 2 mo (n = 13) and 10.33 at 6 mo (n = 6); confidence scores improved from mean of 19.63 at baseline (n = 19) to 28.00 at 2 mo (n = 12) and 29.60 at 6 mo (n = 5)	89% at 2 and 6 mo/ Survey at baseline, 2 mo and 6 mo FU	Activate EMS BLS Needle-based nal admin "Educational and practical skills" (NR/NR)

(Continues)

TABLE 2. Articles Included in Review (Continued)

Authors (Year)	Program Name	Program Site (Location)	Sample Size	Time Frame	Outcomes			Training Content (Duration/Setting)
					Num Nal Admin/Num Indiv Used Nal/Num Witnessed Overdoses	% Survived After Nal/ Change in Knowledge	% Follow Up/ Sources of Outcome Data	
Markham Piper et al. (2008)	Skills and Knowledge on Overdose Prevention	Syringe exchange and harm reduction sites (New York, New York)	122	March 2005–December 2005	82/50/NR	83%/NR	NR/nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Needle-based nal admin Cooperation with police and medical staff Sharing education about nal and overdose with drug-using partners (10–30 min/ indiv, pair, or group of 5–15 people by staff and volunteers plus 1–2 min with physician)
Sherman et al. (2008)	Chicago Recovery Alliance	Syringe exchange program (Chicago, Illinois)	31	3 mo in 2004	18/NR/NR	100%/subjective reports of increased sense of ability to help peers and comfort level with nal admin	NA/qualitative interviews	Overdose prevention Recognize overdose Rescue breathing Prevention of choking and aspiration Needle-based nal admin (30 min/indiv or small group)
Strang et al. (2008a)	NR	20 drug treatment facilities (England)	239	2005–2006	10/10/18	100%/knowledge composite scores increased stat sig from 16.7 pretraining to 21.4 posttraining	78%/pre- and posttraining survey and 3-mo FU survey	Risk factors for overdose Recognize overdose Nal admin Actions to be taken during overdose (NR/NR)
Tobin et al. (2009)	Staying Alive Program	Syringe exchange programs (Baltimore, Maryland)	250	October 2004–April 2005	22/19/51	100%/knowledge of risk factors for OD did not change; knowledge about naloxone improved for 46% of sample	34%/6-mo FU assessment	Overdose prevention Risk factors for overdose Recognize overdose Rescue breathing Recovery position Needle-based nal admin (1 hr/NR)
Wagner et al. (2010)	Homeless Health Care Los Angeles Center for Harm Reduction, Skid Row	Community health care program including syringe exchange (Los Angeles, California)	66	September 2006–January 2008	28/NR/35	NR/stat sig increase in overall knowledge index from a baseline mean of 77% to 3-mo mean of 91%	71%/nal refill form and 3-mo FU interview	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Recovery position Needle-based nal admin Mechanisms of opioid overdose (1 hr/indiv or group of 2–6 people, training by 2 trainers, brief meeting with physician)

(Continues)

TABLE 2. Articles Included in Review (Continued)

Authors (Year)	Program Name	Program Site (Location)	Sample Size	Time Frame	Outcomes			Training Content (Duration/Setting)
					Num Nal Admin/Num Indiv Used Nal/Num Witnessed Overdoses	% Survived After Nal/ Change in Knowledge	% Follow Up/ Sources of Outcome Data	
Walley et al. (2013a)	MA Opioid Overdose Prevention Pilot Program	Addiction treatment programs, HIV prevention programs, syringe exchanges, emergency departments and homeless shelters (MA)	1553	September 2008–December 2010	92/62/NR	100%/NR	51%/nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Intranasal nal admin (5–60 min/indiv or group trainings by public health workers)
Walley et al. (2013b)	MA Overdose Education and Naloxone Distribution Program	HIV education centers, syringe exchanges, substance abuse treatment programs, emergency and primary health care centers, and community meetings (MA)	4857	September 2006–December 2009	545/NR/NR	98%/NR	11%/nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Intranasal nal admin (10–60 min/indiv or group by OOPP trainers)
Yokell et al. (2011)	Preventing Overdose and Naloxone Intervention	Syringe exchange, HIV education center, substance abuse treatment programs, and homeless shelters (RI)	120	2006–NR	5/5/NR	100%/NR	8%/nal refill form and 3-mo FU survey	Overdose prevention Risk factors for overdose Response to overdose Nal admin (NR training by research assistant)

*Six-month follow-up of a subset of participants from Strang et al. (2008).

‡Naloxone was 98% effective, but the 2 individuals for whom it was not effective were subsequently treated by EMS and survived; therefore survival rate was 100%.

Admin, administration; approx, approximately; BLS, basic life support; CPR, cardiopulmonary resuscitation; detox, detoxification; EMS, emergency medical services; FU, follow-up; indiv, individuals; MA, Massachusetts; NA, not applicable; nal, naloxone; NR, not reported; num, number; OD, overdose; OOPP, opioid overdose prevention program; stat sig, statistically significant; RI, Rhode Island; RN, registered nurse.

APPENDIX 3: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives : Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Health, National Prescription Audit Extended

The National Prescription Audit (NPA) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 - 75% (varies by class and geography) of mail service pharmacies and approximately 70-85% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

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