

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

October 5, 2016

kaleo, Inc. Briefing Dossier

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LIST OF ABBREVIATIONS

Abbreviation	Term
ASTM	American Society for Testing and Materials
AUC _{0-t}	area under the concentration-time curve from baseline to the last measurable concentration
AUC _{0-inf}	area under the concentration-time curve from baseline extrapolated to infinity
AUC _{0-T_{max}}	area under the curve from time zero to the T _{max} for each subject in the 2.0 mg IN study arm
C _{max}	maximum plasma concentration
CI	Confidence Interval
CNS	central nervous system
FDA	Food and Drug Administration
g%CV	geometric percent coefficient of variation
HCl	hydrochloride salt
hr	hours
IFU	instructions for use
IEC	International Electrotechnical Commission
IN	intranasal(ly)
IM	Intramuscular(ly)
ISO	International Organization for Standardization
ISTA	International Safe Transit Association
IV	intravenous(ly)
M6G	morphine-6-glucuronide
MedDRA	Medical Dictionary for Regulatory Activities
min	minutes
NDA	new drug application
PK	pharmacokinetics
PIL	patient information leaflet
SC	subcutaneous(ly)
SD	standard deviation
T _{1/2}	terminal-phase elimination half-life
T _{max}	time at maximum plasma concentration
UL	Underwriter Laboratories
USP	United States Pharmacopeia

LIST OF APPENDICIES

- [Appendix 1](#): EVZIO (naloxone HCl injection) Auto-Injector: Prescribing Information April 2014
- [Appendix 2](#): EVZIO (naloxone HCl injection) Auto-Injector: Patient Information / Instructions for Use April 2014
- [Appendix 3](#): Trainer for EVZIO: Trainer Instructions for Use April 2014
- [Appendix 4](#): Opioid Emergencies and Life-Threatening Respiratory Depression: Kaleo, Inc. 2016

1. EXECUTIVE SUMMARY

The purpose of this document is to provide relevant information to the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to support their discussion of naloxone hydrochloride (HCl) products intended for use in the community, specifically the most appropriate dose or doses of naloxone HCl to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in this setting.

Opioid overdose has continued to rise rapidly over the last decade and the recent spikes in heroin overdose deaths and reports of super-potent fentanyl analogs support this as a dynamic public health epidemic. To help combat the morbidity and mortality associated with the opioid overdose epidemic, the Food and Drug Administration (FDA) has encouraged development of new naloxone HCl products for use in the community setting by individuals who lack the medical expertise to titrate a naloxone HCl dose to achieve a desired response. To date, two naloxone HCl products have been approved by the FDA for use in all patient populations in the community setting: EVZIO® (naloxone HCl injection, USP) 0.4 mg auto-injector¹; and NARCAN® (naloxone HCl) Nasal Spray 4 mg. Both products are provided in a carton with two units so that a second dose is available in case the desired response is not observed following the first dose or in case renarcotization occurs before emergency treatment is available.

Additionally, a third product that is used in the community setting is a naloxone HCl injection USP luer-lock prefilled syringe, fitted with a nasal atomizer for intranasal (IN) administration. This product is not FDA approved, and therefore is considered an off label use of this naloxone HCl formulation. [Table 1](#) provides a brief summary of all three products used in the community setting.

Safety of Naloxone HCl Products

Naloxone HCl injection has been used for over 40 years to reverse the effects of opioids and is widely considered a safe drug. Doses well above the original FDA approved (i.e., 1971) initial dose range for parenteral administration (0.4 mg to 2.0 mg) have been administered without significant adverse effects. Risks associated with naloxone HCl are well documented in the literature and in the prescribing information of marketed naloxone HCl products. Naloxone HCl has essentially no effect in individuals not exposed to an opioid, therefore there is little safety risk associated with accidental use of naloxone HCl in someone who isn't suffering from opioid-induced respiratory depression. The most frequent adverse reaction associated with the use of naloxone HCl is precipitated acute withdrawal syndrome in opioid-dependent individuals, which can be life-threatening in neonates. Other serious adverse effects of naloxone HCl include cardiovascular effects, though it is unclear whether these adverse effects are caused directly by

¹ The prescribing information ([Appendix 1](#)), patient information leaflet ([Appendix 2](#)), and trainer instructions for use ([Appendix 3](#)) are included in this dossier.

naloxone HCl, secondary to hypoxemia from the opioid intoxication, or as part of an acute withdrawal syndrome induced by naloxone HCl administration.

Post-marketing safety results for EVZIO further support the safety profile of naloxone HCl use in the community setting. Between July 2014 and April 2016, a total of 275,527 EVZIO auto-injectors were distributed; 162,729 through the kaléo Cares Donation Program and 112,798 through pharmacies and a patient assistance program. The number of adverse events reported (N=15) for EVZIO during this time frame is small. The reported adverse events for EVZIO are discussed in more detail in [Section 3.1.2](#).

Pharmacokinetics of Naloxone HCl in Humans

The FDA approved indication for naloxone HCl injection in adults with known or suspected narcotic overdose is an initial dose of 0.4 mg to 2 mg of naloxone HCl administered intravenously (IV). If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. The pharmacokinetic (PK) data of 2 mg naloxone HCl administered IV and 20 mg administered IN in powder form demonstrate significantly higher naloxone plasma concentrations than those seen with 2.0 mg naloxone HCl administered intramuscularly (IM).

The relative bioavailability of 0.4 mg naloxone HCl administered IM/subcutaneously (SC) to the anterolateral thigh using EVZIO compared to a standard syringe has been established in a study of 30 healthy subjects. EVZIO provides equivalent naloxone AUC and 15% greater naloxone C_{max} in comparison to a single 0.4 mg IM/SC naloxone HCl injection administered using a standard syringe.

The relative bioavailability of NARCAN Nasal Spray to naloxone HCl administered into the *gluteus maximus* muscle using a standard syringe has been established in a study of 29 healthy subjects. 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 HCl administered by IM injection was 46.7%, and 43.9%, respectively. However, in a PK study of 36 volunteers with chronic rhinitis, the relative bioavailability of 2.0 mg naloxone HCl administered IN using a different IN device (off label IN Naloxone Kit) compared to the same dose administered IM using a standard syringe to the anterolateral thigh resulted in a much lower relative bioavailability of approximately 14.6%. The inconsistency in relative bioavailability results for NARCAN and the IN Naloxone Kit may be due to differences in the patient populations studied, location of the IM injection, formulation, IN device delivery performance, or a combination of these factors.

It has been suggested in the literature that abnormal nasal physiology, drug interactions and certain diseases may impact the absorption and bioavailability of drugs administered IN, including naloxone HCl. In a PK study of 36 volunteers with chronic rhinitis, the relative bioavailability of 2.0 mg naloxone HCl administered using an IN Naloxone Kit in the presence and absence of pre-treatment with oxymetazoline HCl 0.05% nasal solution USP (Afrin®, Merck & Co., Inc.) was compared (Study IJ 901DV 03O). The bioavailability of naloxone HCl administered IN after oxymetazoline was lower than naloxone HCl administered IN as

monotherapy with geometric mean ratios (IN+ oxymetazoline / IN) for C_{max} and both AUC_{0-t} and AUC_{0-inf}. The absorption was most prominently impacted during the first hour of absorption. The results from this study demonstrate that administration of a commonly used over-the-counter vasoconstrictor, oxymetazoline, 30 minutes prior to IN naloxone HCl administration had a striking reduction in naloxone plasma concentrations. Sponsors of IN naloxone HCl products should consider evaluating these possible interactions with their products to better inform prescribers and patients of any potential risks.

Selection of Appropriate Doses/Dose Algorithms

To address the opioid epidemic, FDA has encouraged the development of naloxone HCl products for use in the community setting using routes of administration easily performed by a non-medical professional. Selection of the most appropriate dose or doses of naloxone HCl to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in the community setting is complex. Due to differences in relative bioavailability between routes of administration, the most appropriate dose or doses of naloxone HCl to reverse the effects of life-threatening opioid overdose in all ages should be decided separately based on route of administration and clearly explained in the product labeling. The most appropriate dose or doses would apply to all naloxone HCl products within that route of administration.

The most appropriate dose or doses for a given route of administration should provide the best risk/benefit profile for their intended use. Repeat dosing instructions (dosing algorithm) should be easily understood by prescribers, patients and caregivers. Avoiding confusion is critical to ensuring naloxone HCl is administered quickly during an opioid emergency. A dose algorithm that addresses the majority of potential treatment needs within the community (e.g., ages, type of opioids dose of opioid, etc.) would reduce the potential for confusion (e.g., failure or delay to administer naloxone HCl). Rare treatment needs (e.g., opioid-dependent neonates) that are not fully addressed by a dose algorithm may best be addressed in the labeling to avoid confusion.

Selection of the Most Appropriate Intramuscular/Subcutaneous Naloxone HCl Dose for the Community Setting

The recommended initial parenteral dose for currently approved naloxone HCl products is between 0.4 mg and 2.0 mg for adult and pediatric patients.

The current recommended dosing for EVZIO in adult and pediatric patients is:

- An initial dose of 0.4 mg administered IM/SC
- Repeat doses of 0.4 mg administered at 2 to 3 minute intervals until emergency medical assistance arrives

Naloxone HCl is widely regarded as a safe drug. It is well understood that naloxone HCl has no pharmacologic effect in the absence of opioids and that doses far exceeding 2.0 mg have been safely administered in adults and pediatric patients. The most frequent adverse reaction associated with the use of naloxone HCl injection is precipitated acute withdrawal syndrome in

opioid-dependent individuals, which is usually not serious except in neonates where acute withdrawal syndrome can be life-threatening.

As precipitated acute withdrawal syndrome in neonates can be life-threatening, the concern for this patient population could be appropriately addressed through the addition of statements in the prescribing information, such as how FDA has addressed this issue in the NARCAN (naloxone HCl) Nasal Spray.

Post-marketing reports received through April 2016 for the current EVZIO dosing algorithm (i.e., 0.4 mg initial with repeat 0.4 mg doses every 2 to 3 minutes) indicate it is safe and effective for the emergency treatment of opioid overdose. Due to the dynamic nature of the ongoing opioid epidemic, including recent introduction of super-potent fentanyl analogs reportedly requiring more naloxone HCl to reverse, continued monitoring of the safety and effectiveness of EVZIO will be maintained to identify if a higher dose may be warranted.

Selection of the Most Appropriate Intranasal Naloxone HCl Dose for the Community Setting

Selection of the most appropriate IN dose or doses of naloxone HCl to reverse the effects of life-threatening opioid overdose in all ages is more complex due to the possible inconsistencies in relative bioavailability between products (e.g., NARCAN versus IN Naloxone Kit) within that route of administration. This is further complicated by data indicating that abnormal nasal physiology, drug interactions and certain diseases may impact the absorption and bioavailability of naloxone HCl administered IN.

The current recommended dosing for NARCAN in adult and pediatric patients is:

- Place the patient in the supine position, and administer an initial dose of 4 mg IN (which equates to ~ 2 mg IM based on relative bioavailability of IN to IM)
- Repeat doses of 4 mg administered (in alternating nostrils) at 2 to 3 minute intervals until emergency medical assistance arrives.

In the absence of scientific data supporting the need for a different dose or multiple doses of NARCAN, maintaining the current single dose will likely reduce the risk of confusion for the prescriber, patient and their caregiver. Any difference in relative bioavailability of any future IN naloxone HCl product compared to NARCAN may need to be addressed in the labeling of both products to help avoid possible prescriber, patient and caregiver confusion.

Additional Considerations for Naloxone HCl Products used in the Community Setting

To ensure delivery of a safe and effective dose, all naloxone HCl products intended for use in the community setting should have the following general features:

- Widely available, FDA approved;
- Usable by non-medical individuals under the stress of an emergency situation (e.g., intuitive use incorporating human factors engineering principles);
- Easily carried (e.g., convenient; portable);
- Ruggedly designed;
- Capable of providing a safe and efficacious dose of naloxone HCl in the community setting;

- Product and labeling to prompt the user to immediately seek definitive emergency medical attention.

Products intended for use in the community setting need to be designed and tested to prove that they are robust, reliable and intuitive to use by non-trained individuals in an emergency situation. A product that contains a life-saving medication poses significant risk to patients if it cannot be used as directed by the intended user population in the intended setting.

2. BACKGROUND

2.1. Opioid Overdose Epidemic

In the United States (US), unintentional deaths due to drug-related toxicity have been rising rapidly over the last decade. The majority of drug overdose deaths (more than 6 out of 10) involved an opioid. (Centers for Disease Control and Prevention, 2010). In 2014, of 47,055 deaths from drug poisoning, 18,893 were attributed to opioid analgesics, representing 40% of drug poisoning deaths (Centers for Disease Control and Prevention-National Center for Health Statistics, 2015). In addition, heroin-related death rates increased 26% from 2013 to 2014, totaling 10,574 deaths in 2014 (Centers for Disease Control and Prevention, 2015).

Opioid-related toxicity occurs across sex, ethnic, age, and geographic strata and involves both medical and nonmedical opioid use (Beletsky, Rich, & Walley, 2012). Prescription drug abuse and misuse are significant contributors to opioid-related fatalities. On average, there are roughly 136,000 emergency room visits due to prescription opioid overdose and opioid-induced respiratory depression every year. Over 50% of emergency room visits for opioid overdose and opioid-induced respiratory depression result in admission/hospitalization, with an average length of stay of 3.4 days and an average charge of \$31,557 per patient, per visit (Yokell, et al., 2014). Most opioid emergencies occur in homes and are witnessed by close friends, a partner, or family members (World Health Organization, 2014) hence supporting the need for naloxone HCl to be available for administration by non-medical personnel who may be in the best position to intervene quickly before emergency medical services can arrive.

Most recently there has been an increase in reports of overdoses involving heroin-fentanyl combinations and super-potent fentanyl analogs such as acetyl fentanyl, furanylfentanyl and carfentanyl that are up to 100 times more potent than fentanyl and require multiple doses of naloxone HCl to reverse (see <http://www.businessinsider.com/heroin-overdoses-ohio-indiana-kentucky-west-virginia-2016-8>, <http://www.cdc.gov/mmwr/volumes/65/wr/mm6533a2.htm>)

The high rate of opioid-related deaths has led to the establishment of naloxone HCl distribution programs in large cities in the US and abroad. These programs train participants how to recognize the signs of opioid overdose, and how to respond and administer naloxone HCl.

For more information regarding the magnitude of opioid emergencies in the US, please refer to Chapter 2 of Opioid Emergencies and Life-Threatening Respiratory Depression, provided as [Appendix 4](#) of this briefing package.

2.2. Naloxone Products Used in Medical Settings

Naloxone HCl injection has been used for over four decades to reverse respiratory depression associated with acute opioid overdose quickly and effectively without widely reported or serious adverse effects (Buajordet, Naess, Jacobsen, & Brors, 2004) (Sporer & Krahl, 2007) (vanDorp, Yassen, & Dahan, 2007). Naloxone HCl injection, United States Pharmacopeia (USP) (NARCAN®) was originally approved in 1971 by the FDA under the 505(b)1 regulatory (e.g., a full New Drug Application (NDA)) pathway with multiple strengths (0.02 mg/mL, 0.4 mg/mL, and 1 mg/mL) for use as an opioid antagonist for the reversal of opioid overdose. An overdose occurs when the opioid binds to opiate receptors in the brain stem, causing desensitization to rising carbon dioxide levels in the blood and a failure of compensatory respiratory mechanisms. Without intervention, respiratory failure can result. Naloxone competitively displaces the opioid at the opiate receptors, reversing the opioid effects.

At the time of initial FDA approval of naloxone HCl injection, the use of naloxone HCl was predominantly in the hospital setting and the risk of opioid-related toxicity in the community was largely confined to illicit drug users. Since then, the prescription opioid environment has changed, broadening the at-risk population and expanding the settings for the use of naloxone HCl. With wider access to opioids, the number of at-risk individuals has increased, and the risk of opioid-related toxicity is not limited to a traditional overdose definition, i.e., ingestion of an excessive dose. For example, some patients take a legitimately prescribed dose of an opioid indicated for a chronic pain condition that has been refractory to other opioid-sparing treatments, yet still suffer from opioid emergencies characterized by life-threatening respiratory depression necessitating intervention with naloxone HCl. This includes individuals who have comorbidities such as chronic respiratory disease that place them at greater risk for the adverse effects of opioids, as well as individuals who take concomitant medications that affect the PK of the opioid, leading to potentiated effects. In today's environment, opioid use is widespread and the majority of opioid-induced respiratory depression is occurring in the out-of-hospital environment.

FDA Approved Indication for Naloxone HCl Injection for use in medical settings

The FDA approved indication for naloxone HCl products intended for use in medical settings is for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic narcotics, propoxyphene, methadone and certain narcotic-antagonist analgesics: nalbuphine, pentazocine and butorphanol. Naloxone HCl is also indicated for the diagnosis of suspected acute opioid over dosage.

FDA Approved Dosing Information for Naloxone HCl Injection for use in medical settings

In adults with known or suspected narcotic overdose, an initial dose of 0.4 mg to 2 mg of naloxone HCl may be administered IV. 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 HCl have been administered, the diagnosis of narcotic-induced or partial narcotic-induced toxicity should be questioned. Intramuscular or SC administration may be necessary if the IV route is not available.

In children with known or suspected narcotic overdose, the usual initial dose 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 HCl may be administered IM or SC in divided doses. If necessary, naloxone HCl injection can be diluted with sterile water for injection.

In neonates with narcotic-induced depression the usual initial dose is 0.01 mg/kg body weight administered IV, IM, or SC. This dose may be repeated in accordance with adult administration guidelines for postoperative narcotic depression. A product containing 0.02 mg/mL should be used.

Literature Review of Pediatric Dosing Information

The American Academy of Pediatrics' recommended dose of naloxone HCl is 0.1 mg/kg for infants and children from birth to 5 years of age or 20 kg of body weight. For children older than 5 years of age or weighing more than 20 kg, a dose of 2.0 mg may be given. These doses may be repeated as needed to maintain opiate reversal. (American Academy of Pediatrics, 1990) The American Academy of Pediatrics dosing regimen was selected because 0.01 mg/kg dosing in the approved labeling for naloxone HCl injection may not provide opiate reversal in some pediatric patients. The guiding principle of the American Academy of Pediatrics is that naloxone HCl has a wide safety window. The American Academy of Pediatrics note that doses up to 0.4 mg/kg and constant infusion of 0.16 mg/kg/hr have not been associated with naloxone HCl adverse effects.

A retrospective review of the emergency use of naloxone HCl in children (birth – 18 years) suggests that the clinical practice of dosing children mimics the practice for adults (Hasan, et al., 2003). In 79 patients who received IV naloxone HCl either in the emergency department or the pediatric critical care unit for treatment of central nervous system (CNS) and/or respiratory depression known or suspected to be due to opioid effects, the average dose to achieve desired outcome was 1.1 ± 0.76 mg, corresponding to 0.08 ± 0.12 mg/kg. The authors suggest that “incremental doses of 0.01 – 0.02 mg regardless of body weight be used for postoperative patients when full reversal of the opioid effects are not desired. Higher doses (0.1 mg/kg body weight up to a maximum initial dose of 2 mg) may be used in settings of opioid overdose when full and immediate reversal of opioid effects is desired.”

Nearly 60 case studies of severe, opioid-related toxicity in pediatric patients necessitating naloxone HCl intervention have been published (Geib, Badu, Ewald, & Boyer, 2006) (McCarron, Challoner, & Thompson, 1991) (Gourlay & Coulthard, 1983) (Gill, Cousins, Nunn, & Choonara, 1996) (Lewis, Klein-Schwartz, Benson, Oderda, & Takai, 1984) (Hardwick, King, & Palmisano, 1997) (Martin & Rocque, 2011) (Pedapati & Bateman, 2011) (Hasselstrom, Berg, Lofgren, & Sawe, 1989) (Hayes, Klein-Schwartz, & Doyon, 2008). In 16 of those cases, details of naloxone HCl dosing are available. In these reports, naloxone HCl was administered by bolus IV injection, IV infusion or IM injection. Doses were variable, ranging from 0.06 – 1.14 mg/dose. In some cases, the dose level appears to have been selected based on body weight while, in others, fixed doses were administered. All patients required two or more doses, and

total naloxone dose was 0.12 – 7.0 mg. In the 10 patients for whom weight-based dosing is known, individual doses ranged from 0.008 – 0.10 mg/kg. Many authors stressed the need to monitor patients for re-narcotization and to adjust the naloxone HCl regimen to the individual patient's condition and response to treatment. The authors report no medical complications and no apparent naloxone toxicity even at the higher doses.

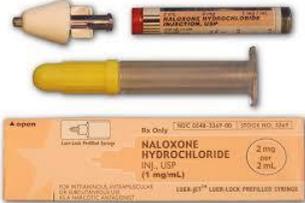
2.3. Naloxone HCl Products Used in the Community Setting

To date, FDA has approved two naloxone HCl products that are specifically designed for use in the community setting by non-medically trained individuals. The first product is EVZIO (naloxone HCl injection, USP) 0.4 mg auto-injector, approved on April 3, 2014. The second product is NARCAN (naloxone HCl) Nasal Spray 4 mg, approved on November 18, 2015. Both of these prescription products were developed under the 505(b)(2) regulatory pathway (i.e., sponsor can rely, at least partially, on the FDA's previous findings regarding safety and efficacy of the original naloxone HCl NDA) as defined in The Federal Food Drug and Cosmetic Act.

The development programs for both products included PK comparisons to a reference naloxone HCl product, manufacturing and stability studies for the new combination product, *in vitro* studies to evaluate the performance of the combination product (according to guidances for auto-injector products and nasal products as appropriate), and Human Factors usability and labeling comprehension studies that take into account use scenarios, critical task success, and representative user populations.

A third product that is commonly used in the community setting is a naloxone HCl injection USP luer-lock prefilled syringe that is fitted with a nasal atomizer for IN administration (off-label IN Naloxone Kit). This product is not FDA approved, and therefore is considered an off label use of this naloxone HCl formulation. [Table 1](#) provides a brief summary of these products including a comparison of the products, dosing instructions and special instructions that are relevant for pediatric use.

Table 1. Naloxone HCl Products Currently Used in the Out of Hospital Setting

Product	EVZIO (naloxone HCl injection, USP) Auto-injector ²	NARCAN (naloxone HCl) Nasal Spray ³	Off-label IN Naloxone Kit ⁴
Manufacturer	kaleo, Inc.	Adapt Pharma, Inc.	Amphastar Pharmaceuticals, Inc. – Naloxone HCl Teleflex Incorporated – MAD Nasal™ intranasal atomizer
Picture of product			
Packaging	Carton containing 2 auto-injectors and 1 Trainer for practice	Carton containing 2 blister packages each with a single nasal spray device	Kit containing naloxone HCl for injection in glass cartridge (capsule) packaged with separate syringe and nasal atomizer
FDA-approved Indication	<ul style="list-style-type: none"> • Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression • Intended for immediate administration as emergency therapy in settings where opioids may be present • Not a substitute for emergency medical care 	<ul style="list-style-type: none"> • Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression • Intended for immediate administration as emergency therapy in settings where opioids may be present • Not a substitute for emergency medical care 	Not Applicable

² EVZIO – naloxone HCl injection, solution. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=df501ed0-c0f4-11e3-8a33-0800200c9a66>

³ NARCAN – naloxone HCl spray. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=724df050-5332-4d0a-9a5f-17bf08a547e1>

⁴ <http://harmreduction.org/issues/overdose-prevention/overview/overdose-basics/understanding-naloxone/>

Product	EVZIO (naloxone HCl injection, USP) Auto-injector ²	NARCAN (naloxone HCl) Nasal Spray ³	Off-label IN Naloxone Kit ⁴
Dosage form	0.4 mg/0.4 mL for IM or SC use only 0.4 mg per dose IM/SC	4.0 mg/0.1 mL for IN use only 4 mg per dose IN	2 mg/ 2mL IN; dose 1 mL per nostril 2 mg per dose IN
FDA Approved Dosing Instructions	<p><u>Initial Dosing</u> 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.</p> <p><u>Dosing in Adults and Pediatric Patients over Age One</u></p>	<p><u>Initial Dosing</u> 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. <u>Repeat Dosing</u> 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.</p>	Not Applicable

Product	EVZIO (naloxone HCl injection, USP) Auto-injector ²	NARCAN (naloxone HCl) Nasal Spray ³	Off-label IN Naloxone Kit ⁴
	<p>Instruct patients or their caregivers to administer EVZIO according to the INSTRUCTIONS FOR USE, intramuscularly or subcutaneously.</p> <p><u>Dosing in Pediatric Patients under Age One</u> In pediatric patients under the age of one, the caregiver should pinch the thigh muscle while administering EVZIO.</p>	<p>Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.</p> <p><u>Dosing Modifications due to Partial Agonists or Mixed Agonist/Antagonists</u> 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 hydrochloride or repeated administration of NARCAN Nasal Spray using a new nasal spray.</p>	
Pediatric use	<ul style="list-style-type: none"> • May be administered to pediatric patients of all ages • In pediatric patients under the age of one, the caregiver should pinch the thigh muscle while administering EVZIO • In neonates and pediatric patients less than one year of age, careful observation of the administration site for evidence of residual needle parts and/or signs of infection is warranted 	<ul style="list-style-type: none"> • May be administered to pediatric patients of all ages • 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 	Not Applicable

Product	EVZIO (naloxone HCl injection, USP) Auto-injector²	NARCAN (naloxone HCl) Nasal Spray³	Off-label IN Naloxone Kit⁴
Features	<ul style="list-style-type: none"> • Auto-retractable needle • No assembly required • Written instructions • Trainer for practice included • Voice and visual instruction system, including audible reminder to seek emergency medical attention 	<ul style="list-style-type: none"> • Needleless • No assembly required • Written instructions • No Trainer for practice included 	<ul style="list-style-type: none"> • Needleless • Assembly required • Written instructions • No Trainer for practice included

3. SCIENTIFIC BACKGROUND

3.1. Naloxone HCl and EVZIO Safety

3.1.1. Literature Review of Naloxone HCl Safety

Naloxone HCl is widely considered a safe drug (Boyer, 2012) (Clarke, Dargan, & Jones, 2005) (Kim, Irwin, & Khoshnood, 2009). Risks associated with naloxone HCl are well-documented in the literature and in the prescribing information of marketed naloxone HCl products.

Naloxone HCl has essentially no effect in non-opioid dependent individuals or individuals not exposed to an opioid, therefore there is little risk of accidental use of naloxone HCl in a subject who isn't suffering from opioid-induced respiratory depression. The most frequent adverse reaction associated with the use of naloxone HCl is precipitated acute withdrawal syndrome in opioid-dependent individuals. Acute withdrawal syndrome can be life-threatening in neonates.

Most of the safety knowledge about naloxone HCl comes from case reports in the literature, which have been the subject of reviews (Clarke, Dargan, & Jones, 2005) (Kim, Irwin, & Khoshnood, 2009). In these reviews, opioid-induced edema can be masked by respiratory depression only to be exposed by naloxone-induced reversal of the respiratory depression. Seizures and arrhythmias are occasionally observed; however, these are known effects of opioid and cocaine use, and it is difficult to separate any effect of naloxone from the effects of these concomitant medications, drugs or pre-existing disease. Cardiovascular side effects of naloxone HCl administration have been described in a review article (Pallasch & Gill, 1981). This review revealed a number of cases with naloxone-induced hypertension, pulmonary edema, atrial and ventricular arrhythmias or cardiac arrest. In all cases, the described adverse cardiovascular effects occurred during naloxone-reversal of opioid anesthesia in a polypharmacy setting; and most of these patients had pre-existing cardiac abnormalities.

A prospective safety study conducted in subjects admitted to the emergency department with heroin intoxication suggested that serious complications from naloxone HCl administration are uncommon (Osterwalder, 1996). In this study, 6 of 453 subjects experienced severe side effects within 10 minutes of naloxone HCl administration, which included one case of asystole, three generalized convulsions, one pulmonary edema and one violent behavior. It is not known whether these adverse effects were caused directly by naloxone HCl, secondary to hypoventilation/hypoxemia from the heroin intoxication, as part of an acute withdrawal syndrome induced by naloxone HCl administration, concomitant medications or concurrent diseases. However, in a literature review of the Osterwalder study, it is noted that an episode of pulmonary edema could be explained by the toxicity of the heroin, three convulsions could be explained by cerebral hypoxia or the withdrawal syndrome, and an episode of violent behavior could be explained by the intensely unpleasant experience of sudden opioid withdrawal. Thus, none of the adverse effects reported by Osterwalder can be attributed reliably to naloxone toxicity. (Baca & Grant, 2005)

In a study of naloxone HCl use in the out-of-hospital setting, 3 out of 1192 overdoses led to adverse events requiring hospitalization (Buajordet, Naess, Jacobsen, & Brors, 2004).

Extremely high doses of naloxone HCl have been administered in clinical trials with minimal toxicity reported (Groeger & Inturrisi, 1987) (Bracken, et al., 1990) (Olinger, et al., 1990) (Adams Jr, et al., 1986). Single SC doses of up to 24 mg of naloxone HCl have been administered without significant signs of toxicity (Gilman, Rall, & Nies, 1990). In a dose escalation study of naloxone HCl for treatment of patients with acute cerebral ischemia, loading doses 0.6 mg/kg to 5 mg/kg followed by a 24-hour infusion resulted in total naloxone HCl exposure of 52 mg to 4978 mg (Adams Jr, et al., 1986). Nausea and vomiting, not dose related, were observed in 12/27 (44%) patients, but 7 of those patients had nausea and/or vomiting prior to receiving naloxone HCl. Other possibly related adverse events were transient elevation in bilirubin (3/27, 11%), confusion (2/27, 7%), hypertension (1/27, 3%) and hypotension/pallor/diaphoresis (1/27, 3%). The bolus doses used in this study were approximately 10 to 1000 times a 0.4 mg dose, and the total naloxone HCl exposure (over the 24 hours in which these adverse events were observed) was up to three orders of magnitude higher than a 0.4 mg EVZIO dose.

3.1.2. EVZIO Post-Marketing Safety Surveillance

EVZIO was approved by the FDA on April 3, 2014 and began commercial distribution in July 2014. There are two main channels for distribution of EVZIO: (1) traditional pharmacy distribution (including patient assistance programs); and (2) donation programs. Kaleo, Inc. has established an extensive donation program to provide EVZIO to the harm reduction community, municipalities, and other stakeholders outside traditional pharmacy distribution channels. Since October 2014 (just shortly after EVZIO became available), kaleo, Inc. has donated EVZIO auto-injectors to over 250 first responder agencies, public health departments and non-profit community groups across 34 states as part of the kaléo Cares Product Donation Program.

The number of packages (NDC 60842-030-01) distributed from July 2014 through April 3, 2016 is provided in [Table 2](#). Since each package of EVZIO contains two auto-injectors and one Trainer for EVZIO, the number of individual auto injectors in distribution is also provided.

In the time frame from FDA approval through April 2, 2016, 15 spontaneous adverse events have been received. These reports are summarized in [Table 3](#). The reported adverse events are consistent with the known safety profile of naloxone HCl. The four case reports of “drug ineffective” included one case where an adult patient was administered two EVZIOs and three IN naloxone doses before he responded with restored breathing; two cases where the adult patients did not respond to cardiopulmonary resuscitation and a single administration of EVZIO by a police officer; and one case of possible user error.

To date there are no safety trends that impact labeling for EVZIO.

Table 2. United States Distribution Information for EVZIO

Distribution Channel	Number of Packages	Number of Auto Injectors
Kaléo Cares Donation Program	81,363	162,729
Pharmacy / Patient Assistance Program	56,399	112,798
Total	137,762	275,527

Table 3. Spontaneous Adverse Event Reports for EVZIO

System Organ Class	Reaction Terms (MedDRA Preferred Terms)	Number Reported (%)*
General disorders and administration site conditions	Drug ineffective	4 (0.0015%)
	Drug withdrawal syndrome	1 (0.0004%)
	Application site erythema	1 (0.0004%)
	Pain	1 (0.0004%)
Psychiatric disorders	Disorientation	3 (0.0011%)
	Anger	1 (0.0004%)
	Confusional state	1 (0.0004%)
	Agitation	1 (0.0004%)
Injury, poisoning, and procedural complications	Accidental exposure to product	2 (0.0007%)

* as a percentage of auto-injectors distributed

3.2. Preclinical Pharmacokinetics

Naloxone is essentially a pure opiate antagonist, exhibiting no agonist activities even at very high concentrations. Naloxone is thought to act as a competitive antagonist at the mu, kappa, and delta opiate receptors in the CNS. It can be classified as an inverse antagonist because it suppresses basal levels of constitutive activity of the receptors that have been pre-treated with agonists, though it does not suppress un-stimulated basal receptor activity (Wang, Sun, & Sadee, 2007) (Liu & Prather, 2001). Inverse antagonists such as naltrexone and naloxone are highly potent for reversing the analgesic and lethal effects of opioid overdose.

3.2.1. Absorption

Naloxone is rapidly mobilized from the injection site. In a study of [¹⁴C] labeled naloxone injected at 10 mg/kg into the rat, 82% of the radioactivity disappeared from the injection site by 0.5 hour and >99% had disappeared by 2 hours. Naloxone quickly located into the brain, with peak radioactivity being detected by 0.25 hours (Misra, Pontani, Vadlamani, & Mule, 1976). Although naloxone is absorbed after oral administration, it is subject to first-pass metabolism and

therefore exhibits a significantly reduced potency compared to naloxone administered by injection (Weinstein, Pfeffer, & Schor, 1974).

Naloxone is a short acting antagonist due to a relatively short half-life. Rats treated IV with naloxone HCl demonstrated very rapid decay in serum naloxone with a half-life of approximately 4 minutes and a distribution phase half-life (between hours 1 and 4 post dose) of approximately 30 minutes. Concentrations of naloxone in the brain were higher than serum, but demonstrated a parallel decay and therefore similar half-life (Ngai, Berkowitz, Yang, Hempstead, & Spector, 1976) (Figure 1). In two studies conducted in dogs, IV administration of naloxone HCl demonstrated serum half-lives in the distribution phase of 56 minutes in one study and 71 minutes in the other (Garret, Shyu, & Ulubelen, 1986) (Pace, RG, MM, Wong, & Blatnic, 1979).

Figure 1. Serum and Brain Concentrations of Naloxone in the Rat after Intravenous Administration

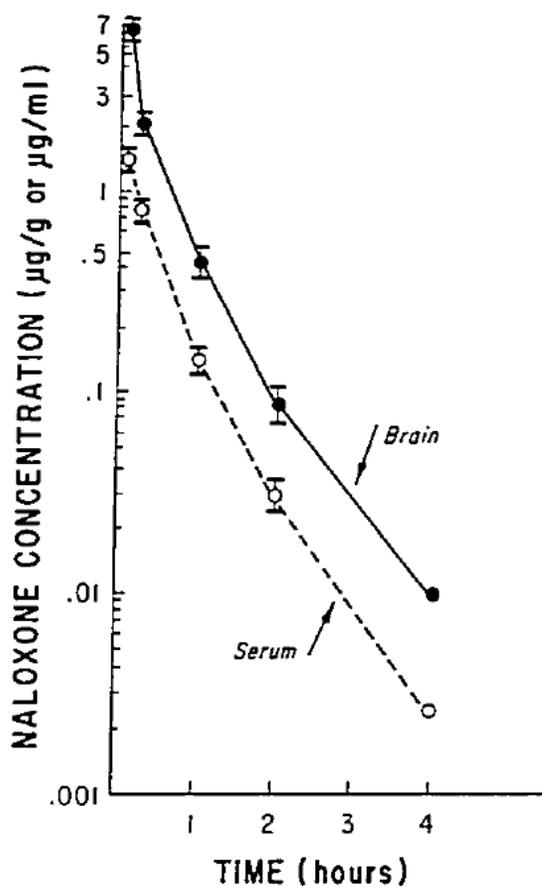


FIG. 1. Serum and brain concentrations of naloxone in rats at intervals following iv injection, 5 mg/kg. Each point represents the mean for 3-5 animals. Vertical bars are SE. Note the higher brain concentrations of naloxone and the parallel decline of drug concentrations with time.

SOURCE: (Ngai, Berkowitz, Yang, Hempstead, & Spector, 1976)

Naloxone demonstrates a rapid entry into the brain that results in a concentration that is higher than the concentration in the serum. Naloxone exhibits both a passive diffusion and a carrier-mediated transport across the blood-brain barrier (Suzuki, et al., 2010). Serum naloxone is quickly eliminated; consequently, as naloxone diffuses from the brain to serum, it is quickly eliminated (Berkowitz, Ngai, Hempstead, & Spector, 1975). There is a marked difference in the brain/plasma ratio of morphine compared to naloxone even though the two compounds show similar half-lives from hours 1 to 4. (Figure 2) (Berkowitz B. A., 1976). Since brain concentrations of naloxone are likely critical in terms of naloxone's ability to antagonize opioid activity, the fast elimination from serum and brain during the distribution phase explain the need to give multiple injections of naloxone HCl. Peak brain levels of morphine were sustained for up to 2 hours, while the brain concentrations of naloxone declined 50% in the first hour (even though it achieved higher overall brain concentrations). Therefore, the PK profile of naloxone, especially the rate of diffusion from the brain, helps explain the observation that multiple injections of naloxone, separated in time, are required to fully counter the analgesic effects of some opioids (Berkowitz B. A., 1976).

Figure 2. Pharmacokinetic Profile of Morphine and Naloxone in the Rat

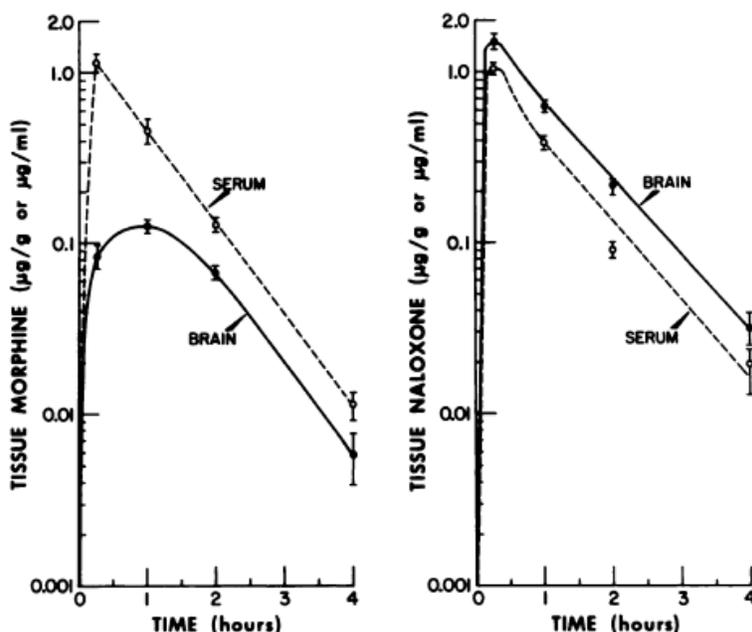


FIG. 3. Comparative brain and serum disposition of naloxone and morphine in rats after a dose of 5 mg/kg s.c. Results are the average \pm S.E. of three to five rats at each time interval.

SOURCE: (Berkowitz, Ngai, Hempstead, & Spector, 1975)

3.2.2. Distribution

Following parenteral administration, naloxone is rapidly distributed into body tissues and fluids. In rats, injection of [14 C]-labeled naloxone is observed in the brain, kidney, spleen, lung, heart, skeletal muscle, and liver. Naloxone is quickly metabolized and at 6 hours most of the dose is not detected in significant amounts in the heart, lung, or muscle. Residual radioactivity is

detected in the liver and kidney, consistent with excretion of naloxone and its metabolites in the urine and feces. In the first 24 hours, 39.6% of the radioactivity was excreted in the urine, while during the 24 to 96 hour period 3.7% was detected in the urine. Over the 0 to 96 hour time course, 20.9% was present in the feces. This represented 64.2% of the total administered dose. The remainder of the radioactivity, 35.8%, was presumed to be N-dealkylated and conjugated N-dealkylated metabolites. (Misra, Pontani, Vadlamani, & Mule, 1976).

Naloxone is weakly bound to plasma proteins (mainly albumin). In human adults, the percentage of naloxone bound to proteins is 54% which is similar to fetal plasma which is about 62% (Asali & Brown, 1984).

In a study conducted in dogs, IV bolus administration of 0.47 and 4.7 mg/kg of naloxone, demonstrated two sequential half-lives of approximately 11 minutes and 56 minutes, respectively. In the dog, the total body clearance of naloxone, 1334 ± 133 mL/min, was slightly higher than that of naltrexone, 1043 mL/min, and was significantly higher than that for morphine doses <0.5 mg/kg, which were 701 mL/min. These differences in volumes of distribution, resulting in the same relative sequence of clearances, could be attributed to the relative lipophilicities of the compounds which have been assigned the order: naloxone $>$ naltrexone $>$ morphine (Garret, Shyu, & Ulubelen, 1986).

3.2.3. Metabolism (Interspecies Comparison)

In the rat, naloxone is nearly completely metabolized with naloxone-3-glucuronide being the main metabolite. Other minor metabolites include: naloxone-3-sulfate, naloxol and conjugated naloxol, 7,8-dihydro-14-hydroxynormorphine, 7,8-dihydro-14-hydroxynormorphine and their conjugates (Misra, Pontani, Vadlamani, & Mule, 1976).

In the dog, naloxone is also subject to almost complete metabolism; the percentage of unchanged naloxone in the urine of dogs was 4.4%. In the dog, no 6β -naloxol or its conjugate was identified (Garret, Shyu, & Ulubelen, 1986). Conjugated naloxone was excreted in the urine at 22 – 46% of the dose. The remainder of the naloxone was metabolized, mostly to conjugates and was secreted in the bile.

Metabolism of naloxone in the rat and dog is similar to human metabolism. In man, glucuronide formation is the dominant form of metabolism, but N-dealkylation and reduction of the 6-keto group are evident in small quantities. Both naloxol (alpha and beta) and the products of the reduction of the 6-keto group are also opioid antagonists. 7,8-dihydro-14-hydroxynormorphine and 7,8-dihydro-14-hydroxynormorphine have been isolated in human urine after receiving large doses of oral naloxone. These dealkylated forms on naloxone also have very little opioid activity (Weinstein, Pfeffer, & Schor, 1974).

3.2.4. Excretion

In rats, dogs, and humans, naloxone is almost completely metabolized. Very low amounts of naloxone, 4.4% in the dog, are secreted as unchanged drug in the urine. After metabolism, most abundantly by conjugation, the metabolized naloxone is excreted in the urine or in bile.

3.3. Clinical Pharmacokinetics and Pharmacodynamics

The prescribing information for naloxone HCl injection products intended for use in medical settings recommends an initial dose of 0.4 to 2.0 mg given IV (or via IM/SC administration if IV administration is not an option). FDA has advised sponsors that a product intended for use in the community setting should meet or exceed the minimally efficacious parenteral dose of 0.4 mg. While IV routes serve as the “gold standard” for absolute bioavailability, this route is not readily available for products intended for the community setting.

Naloxone HCl is poorly orally bioavailable, approximately 2%, and is poorly available by rectal administration, approximately 15% (Smith, et al., 2012). Therefore, naloxone HCl has traditionally been administered by parenteral administration. Due to this, comparisons to the reference naloxone HCl product have been made using the more accessible IM route.

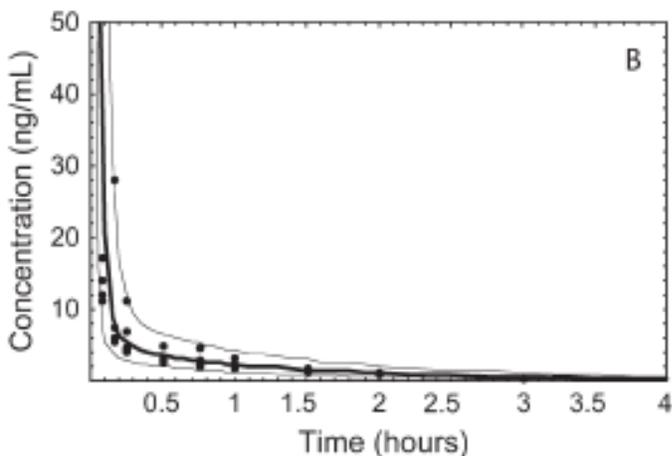
The PK of naloxone is best described by a two-compartment model (Yassan, et al., 2007) (Dowling, Isbister, Kirkpatrick, Naidoo, & Graudins, 2008). Naloxone is rapidly distributed in the body and disappears over a period of approximately 15 to 20 minutes from the serum in the initial distribution phase. The elimination half-life is estimated to be between 30 to 90 minutes (Goldfrank, Weisman, Errick, & Lo, 1986) (Berkowitz B. A., 1976) (Berkowitz, Ngai, Hempstead, & Spector, 1975).

Dowling and his colleagues published population PK for naloxone HCl administered via IV, IM, and IN routes. The relative bioavailability of IM administered naloxone HCl was 36% compared to IV administered naloxone, while the relative bioavailability on IN administered naloxone HCl was 4%, but the authors note that this estimate was likely impacted by the dilute formulation used in the studies.

3.3.1. Pharmacokinetics of Intravenous Administration of Naloxone HCl

Naloxone HCl is considered to have an excellent safety profile and large amounts can be administered without significant adverse effects in humans. Dowling and colleagues published the PK profile of IV naloxone using 2 mg naloxone HCl (Dowling, Isbister, Kirkpatrick, Naidoo, & Graudins, 2008) as shown in [Figure 3](#).

Figure 3. Naloxone Plasma Concentration-Time Profiles Following Intravenous Administration of 2 mg Naloxone HCl



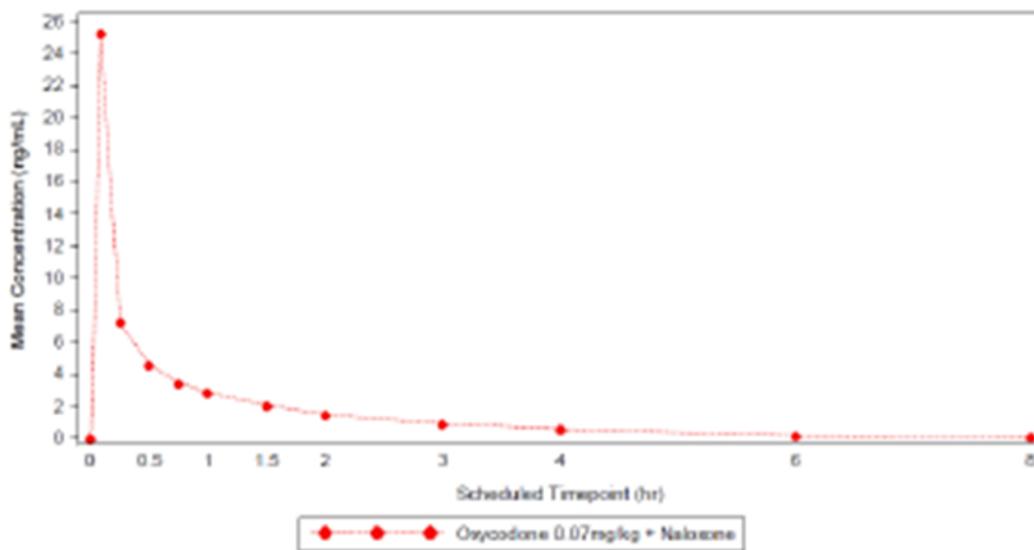
SOURCE: FIGURE 2 FROM (Dowling, Isbister, Kirkpatrick, Naidoo, & Graudins, 2008)

The safety of naloxone HCl has been utilized by pharmaceutical companies in efforts to create abuse-deterrent formulations of opioids. In this formulation strategy, an amount of naloxone HCl that would inhibit opioid responses is provided with the intended opioid for oral administration. Because naloxone HCl has poor oral bioavailability, the naloxone is weakly absorbed while the intended opioid is more readily absorbed from the gastrointestinal track. If, however, the product is subjected to misuse through an attempted IN or parenteral route of administration, the excess naloxone inhibits the opioid activity in the formulation. For example, TARGINIQ® ER (oxycodone HCl and naloxone HCl) tablets contain a 2:1 ratio of oxycodone: naloxone with the largest strength tablet containing 40 mg oxycodone and 20 mg naloxone. As part of the development of this product, the PK of naloxone was evaluated under IV conditions in which parenteral formulations were produced that mimicked the tablet formulation.

In the study, 24 participants received 0.07 mg/kg oxycodone and 0.035 mg/kg naloxone IV and the PK profile of naloxone is shown in [Figure 4](#). Mean (\pm SD) PK parameters included C_{max} (25,270 [\pm 11,690] pg/mL), AUC_{0-t} (12,630 [\pm 2530] h-pg/mL), AUC_{0-inf} (12,730 [\pm 2550] h-pg/mL) and T_{max} (0.05 hour).

These two studies demonstrate that IV administration of 2 mg or more of naloxone HCl is safe with an early exposure (C_{max}) much higher than comparable products intended for use in the community setting.

Figure 4. Naloxone Plasma Concentration-Time Profiles Following Intravenous Administration of 0.035 mg/kg Naloxone HCl



SOURCE: (FDA -TARGINQ ER SBA, 2014)

3.3.2. Pharmacokinetics of Naloxone HCl Administered Intramuscular/Subcutaneous

A randomized, single-dose, single-blind, two-sequence, two-period crossover bioavailability, safety and tolerability study in 30 healthy human subjects was conducted to evaluate the bioavailability and PK of a single IM/SC injection of 0.4 mg naloxone HCl for injection administered in the thigh using EVZIO and 0.4 mg naloxone HCl for injection (USP) [1 mg/mL] (International Medication Systems, Ltd, an Amphastar Pharmaceuticals Company) administered IM/SC in the thigh using a standard syringe. Subjects were randomized to treatment sequence and received treatments on consecutive days as in-patients. Both EVZIO and the standard syringe (5/8" 23-gauge needle) have a set needle length, therefore the injections were either IM or SC depending on the tissue layer thickness of the subject (i.e., the amount of fat overlying the muscle). Blood was collected prior to dosing and for 6 hours post-dose for each dosing period. Both total naloxone (e.g., naloxone and its main metabolites) and plasma naloxone were determined. Pharmacokinetic parameters were calculated.

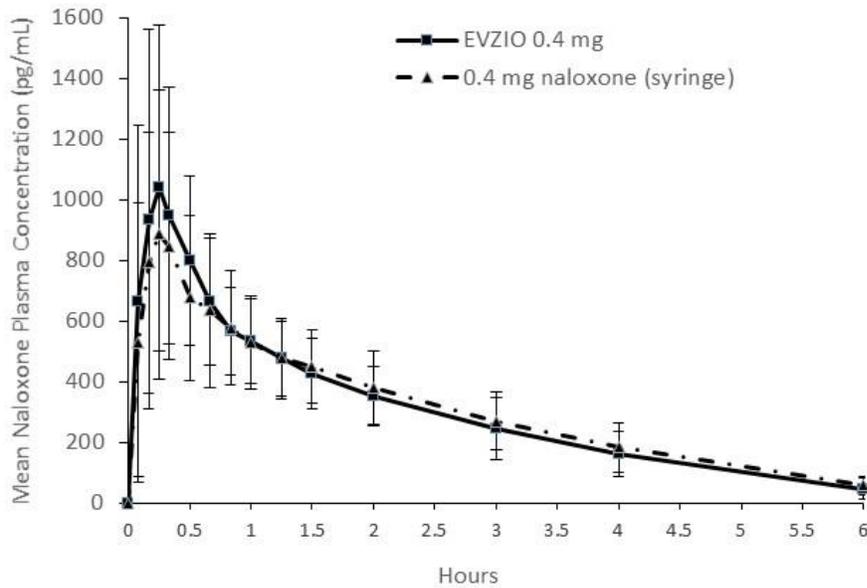
Naloxone concentrations and PK profiles of total naloxone and plasma naloxone were comparable, and only plasma naloxone data are included in this briefing document. Mean naloxone plasma concentration data at each nominal time point are displayed graphically in [Figure 5](#). Pharmacokinetic parameters and the statistical analysis of relative bioavailability are provided in [Table 4](#).

For both AUC_{0-t} and AUC_{0-inf} , EVZIO 0.4 mg is bioequivalent to the reference naloxone HCl product using standard statistical techniques. A slightly higher C_{max} is observed following EVZIO 0.4 mg injection compared to the reference naloxone HCl product. Median T_{max} and

median $T_{1/2}$ were similar after dosing with EVZIO 0.4 mg compared to the reference naloxone product (IMS/Amphastar). Both products were well tolerated by the subjects in this study.

In summary, a single injection of naloxone HCl 0.4 mg administered via EVZIO was found to have comparable bioavailability to a single injection of the reference 0.4 mg naloxone HCl product administered with a standard syringe.

Figure 5. Mean (\pm SD) Naloxone Plasma Concentration-Time Profiles Following Intramuscular/Subcutaneous Administration of 0.4 mg Naloxone HCl



SOURCE: IJ-900DV-03O CLINICAL STUDY REPORT

Table 4. Summary of Naloxone Plasma Pharmacokinetic Parameters and Comparative Bioavailability Results (Study IJ-900DV-03O)

Treatment	Statistic	C _{max} (pg/mL)	T _{max} (h)	T _{1/2} (h)	AUC _{0-t} (pg-h/mL)	AUC _{0-inf} (pg-h/mL)
Pharmacokinetic Parameters						
EVZIO (0.4 mg naloxone)	Geometric Mean (g%CV)	1100 (52.4)		1.22 (29.2)	1780 (23.1)	1880 (24.7)
	Median (Min-Max)	1070 (471-3110)	0.25 (0.08-1.23)	1.20 (0.885-3.13)	1790 (898-2680)	1910 (932-2960)
Reference – syringe (0.4 mg naloxone)	Geometric Mean (g%CV)	957 (53.2)		1.32 (22)	1800 (26.9)	1910 (27.5)
	Median (Min-Max)	959 (294-2270)	0.33 (0.08-2.03)	1.28 (0.894-2.35)	1760 (859-3040)	1840 (922-3100)
Comparative Bioavailability Results						
Treatment Ratio	EVZIO/ Reference	1.15			0.993	0.983
	90% CI for ratio	0.97, 1.37			0.94, 1.05	0.94, 1.03

SOURCE: IJ-900DV-03O CLINICAL STUDY REPORT

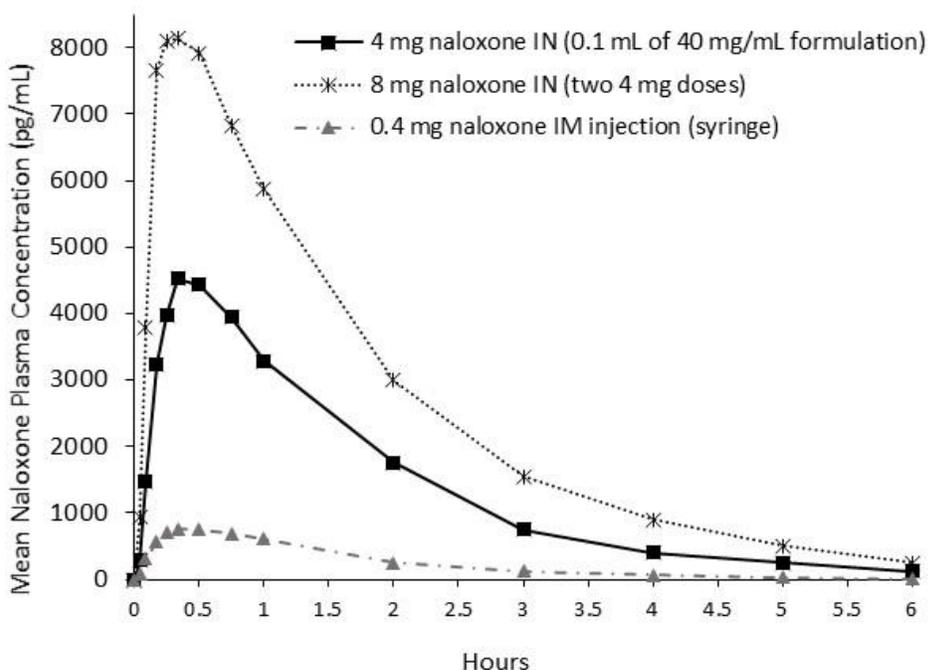
3.3.3. Pharmacokinetics of Naloxone HCl Administered Via the Intranasal Route**3.3.3.1. Pharmacokinetics of Naloxone HCl Powder Administered via the Intranasal Route**

In a PK study of 24 healthy adult recreational opioid users with a history of IN abuse TARGINIQ® ER (40 mg oxycodone HCl and 20 mg naloxone HCl) was crushed into a powder and inhaled through the nostrils to mimic IN abuse. Mean (\pm SD) PK parameters included C_{max} (20,150 [\pm 5710] pg/mL), AUC_{0-t} (29,600 [\pm 12500] pg-h/mL, AUC_{0-inf} (29,930 [\pm 12470] pg-h/mL) and T_{max} (median 0.28 hour [range 0.3-0.73]). The PK profile of naloxone is shown in [Figure 6](#).

The early exposure (C_{max}) for 20 mg of naloxone HCl crushed into powder was similar to 2 mg naloxone HCl administered IV, while the overall naloxone exposure (AUC) was more than two times the amount seen for 2 mg naloxone HCl administered IV. This is an additional demonstration that large doses of naloxone HCl can be safely administered in adult recreational opioid users.

46.7%, and 43.9%, respectively. Mean naloxone plasma concentration-time profiles are presented in Figure 7 (N=29).

Figure 7. Mean Naloxone Plasma Concentration-Time Profiles Following Intranasal Administration of Naloxone HCl (NARCAN Nasal Spray)



SOURCE: (FDA - NARCAN SBA, 2015); (Krieter, et al., 2016)

3.3.3.3. *Relative Bioavailability of Intranasal Administration of Naloxone HCl using a Mucosal Atomization Device to Intramuscular Administration using a Standard Syringe*

The IMS Ltd./Amphastar 1 mg/mL naloxone HCl injection USP product is also being used in the out-of-hospital setting via IN administration using an off-label kit that includes a naloxone cartridge, syringe and nasal atomizer (see Table 1). The off-label Naloxone IN Kits have been primarily distributed and used by first responders, police, and members of some harm reduction clinics who receive training on the use of the kits and IN delivery of naloxone, primarily for heroin overdose emergencies. An increasing number of retail pharmacists are also dispensing off-label Naloxone IN Kits in the community. The off-label use of parenteral naloxone HCl in off-label Naloxone IN Kits without supporting PK and efficacy data is debated in a recent article (Strang & McDonald, 2016).

In a PK study of 36 adult patients with chronic rhinitis, the relative bioavailability of two 1 mg nasal sprays (2.0 mg total dose, 1 mL of 1 mg/mL naloxone HCl solution, 1 spray per nostril)

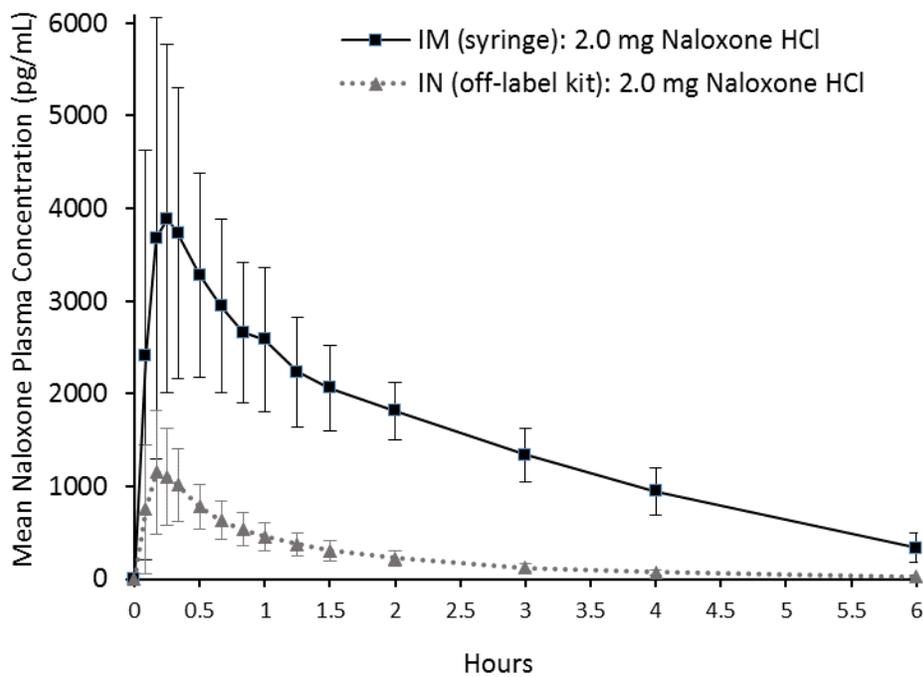
using the off-label IN Naloxone Kit was compared to a single dose of 2.0 mg naloxone HCl IM injection in the anterolateral aspect of each thigh. Eligibility criteria included a diagnosis of chronic rhinitis but no other nasal abnormalities⁵. Geometric mean (g%CV) PK parameters for the IN Naloxone Kit were C_{\max} (1163 [47.5] pg/mL), T_{\max} (0.25 hour [median]), half-life (1.44 [17.2] hours), and AUC_{0-t} and AUC_{0-inf} (1381 [35.4] and 1411 [35.7] pg-h/mL, respectively). Geometric mean (g%CV) PK parameters for the standard syringe were C_{\max} (4150 [43.9] pg/mL), T_{\max} (0.25 hour [median]), $T_{1/2}$ (1.47 [24.4] hours), and AUC_{0-t} and AUC_{0-inf} (9317 [13.6] and 9669 [13.8] pg-h/mL, respectively).

In this study, the relative bioavailability of naloxone administered IM was higher than naloxone administered IN with geometric mean ratios (IM / IN) of 3.57 for C_{\max} and 6.75 and 6.85 for AUC_{0-t} and AUC_{0-inf} , respectively. The relative bioavailability of this formulation administered IN compared to IM using a standard syringe is approximately 14.6%. The naloxone plasma concentration-time profile for 2.0 mg administered IN using an off-label IN Naloxone Kit relative to 2.0 mg administered IM using a standard syringe is shown in [Figure 8](#).

These results further indicate that naloxone HCl administered IN requires higher doses to achieve plasma naloxone levels comparable to those observed with the same naloxone HCl dose administered IM. The inconsistency of these relative bioavailability results (i.e., 14.6%) and those observed for NARCAN (i.e., 46.7%) in [Section 3.3.3.1](#) may be due to differences in the patient populations studied, location of IM injection, formulation, IN device delivery performance, or a combination of these factors.

⁵ The inclusion criteria for chronic rhinitis was due to a third study arm comparing drug-drug interactions of IN naloxone HCl and the over-the-counter vasoconstrictor, oxymetazoline (See [Section 3.3.3.4](#)).

Figure 8. Mean (\pm SD) Naloxone Plasma Concentration-Time Profiles of 2.0 mg Naloxone HCl Administered Using an Intranasal Naloxone Kit and Intramuscular Using a Standard Syringe



SOURCE: IJ-901DV-03O CLINICAL STUDY REPORT

3.3.3.4. Potential Nasal Physiology and Drug Interactions that may Impact Intranasal Absorption of Naloxone HCl

Drugs administered IN are absorbed via the nasal mucosa and rapidly enter systemic circulation (Robinson & Wermeling, 2014), suggesting this is a useful mode of administration for a medication used in life-threatening emergency situations. However, abnormal nasal physiology (e.g., intranasal damage caused by substance abuse, excessive nasal mucus, nasal trauma), drug interactions and certain diseases may impact the absorption and bioavailability of drugs administered IN, including naloxone HCl.

Barton et al, conducted a study in which trained emergency medical services personnel administered atomized naloxone HCl to patients and observed them for any opioid-reversing effects before application of naloxone HCl IV. In this study there were nine patients (17%) who did not respond to naloxone HCl administered IN and required rescue IV naloxone. Five of the nine patients had some nasal physiological changes (epistaxis [2], nasal mucus [1], trauma [1], or septal abnormality [1]) (Barton, et al., 2005); suggesting nasal physiology may play a role in the effectiveness of IN administered naloxone HCl.

Concomitant medications may also have an impact on the absorption of naloxone administered IN. Davis et al and Shyu et al reported that in patients experiencing rhinitis, use of a

vasoconstrictor prior to IN administration of opioids with chemical structures similar to naloxone HCl (hydromorphone and butorphanol), resulted in delayed absorption and reductions in C_{max} (Davis, Rudy, Archer, Wermeling, & McNamara, 2004) (Shyu, Pittman, Robinson, & Barbhैया, 1993).

In a PK study of 36 volunteers with chronic rhinitis the relative bioavailability of 2.0 mg naloxone HCl administered using an IN Naloxone Kit in the presence and absence of pre-treatment with oxymetazoline HCl 0.05% nasal solution USP (Afrin[®], Merck & Co., Inc.) was compared (Study IJ-901DV-03O). Afrin is a commonly used over-the-counter nasal vasoconstrictor.

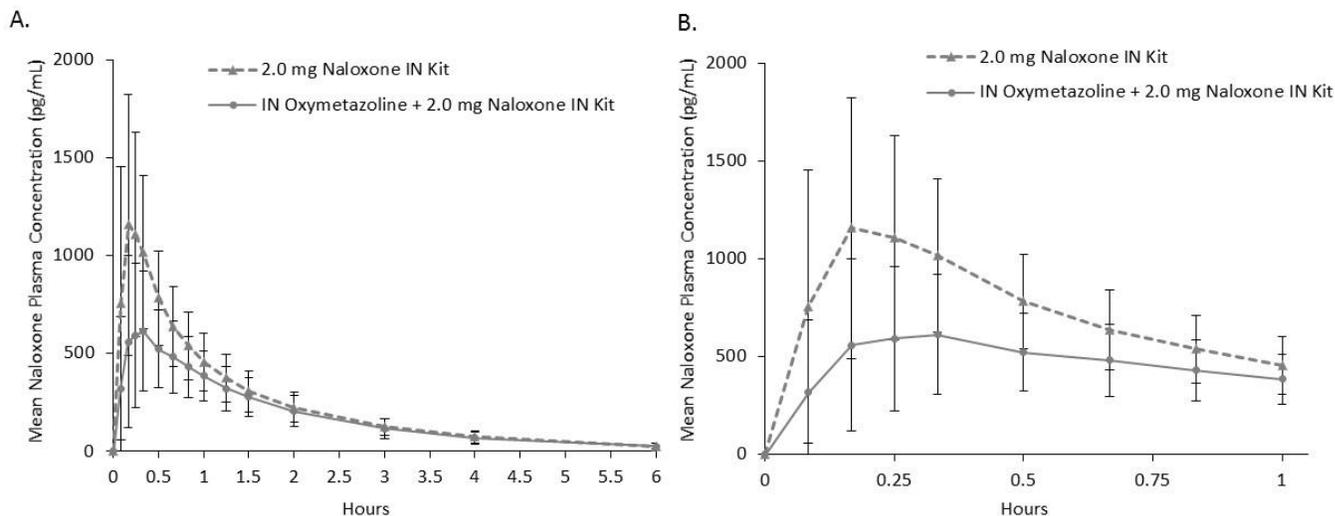
For the nasal vasoconstrictor treatment arm, subjects received 6 sprays (divided into 3 sprays per nostril) of oxymetazoline per product labeling 30 minutes prior to IN administration of 2.0 mg naloxone HCl. PK parameter results are in [Table 5](#) and the naloxone plasma concentration-time profiles are in [Figure 9](#).

The bioavailability of naloxone HCl administered IN after oxymetazoline was lower than naloxone HCl administered IN as monotherapy with geometric mean ratios (IN + oxymetazoline /IN) of 0.58 for C_{max} and 0.78 for both AUC_{0-t} and AUC_{0-inf} . The absorption was most prominently impacted during the early-phase absorption (0.38; see AUC_{0-Tmax} in [Table 5](#)).

Administration of the vasoconstrictor 30 minutes prior to naloxone HCl administration resulted in a striking reduction in naloxone plasma concentrations. It is reasonable to expect that other vasoconstricting agents such as cocaine are likely to have a similar impact. Given the half-life of oxymetazoline is 5 to 8 hours, the potential for this drug interaction to last for an extended period of time after administration of the vasoconstrictor should be expected and may impact the need for higher or repeat IN naloxone HCl dosing.

The variability in naloxone exposure due to drug interactions and variations in nasal physiology should be considered during formulation of an IN naloxone HCl product to ensure that during the early critical period of naloxone absorption, at least minimal expected naloxone exposure is achieved. This variability should also be evaluated to determine if appropriate patient populations and use scenarios should be defined for IN naloxone HCl. Sponsors should consider evaluation of PK for IN products in subjects with different nasal physiology and in drug-interaction studies. Product labeling should reflect dosing adjustments or warnings for conditions where reduced absorption is noted for such products.

Figure 9. Mean (\pm SD) Naloxone Plasma Concentration-Time Profiles following Intranasal Administration of 2.0 mg Naloxone with and without Vasoconstrictor Pre-treatment, (A) 0-6 hour and (B) 0-1 hour



SOURCE: IJ-901DV-030 CLINICAL STUDY REPORT

Table 5. Comparison of Intranasal 2.0 mg Naloxone HCl Pharmacokinetics in Subjects with Chronic Rhinitis with and without Concomitant Nasal Vasoconstrictor Use

Parameter Geometric Mean (g%CV)	Study IJ-901DV-030, N=36	
	2.0 mg IN Naloxone Kit	2.0 mg IN Naloxone Kit + oxymetazoline
C _{max} (pg/mL)	1163 (47.5)	671 (48.9)
T _{max} (h)	0.25 (0.07, 0.68)	0.33 (0.08, 1.0)
T _{1/2} (h)	1.44 (17.2)	1.46 (20.7)
AUC _{0-t} (pg-h/mL)	1381 (35.4)	1051 (35.4)
AUC _{0-inf} (pg-h/mL)	1411 (35.7)	1077 (35.3)
AUC _{0-Tmax} (pg-h/mL)	144 (75.1)	55 (197.6)

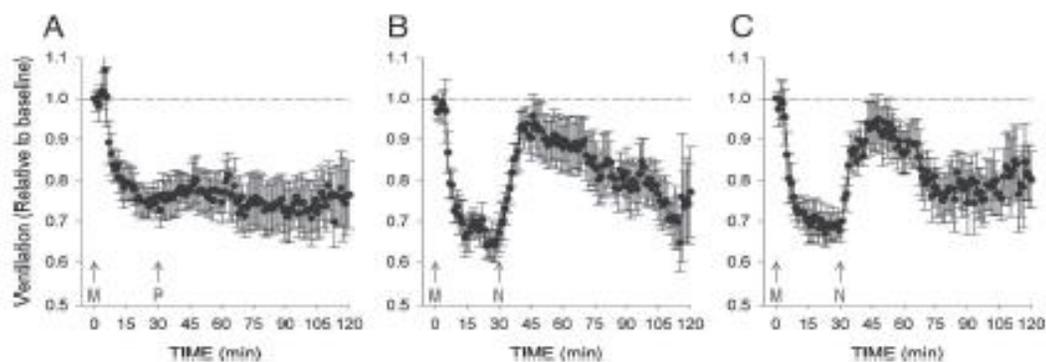
Note: T_{max} data are medians and ranges; AUC_{0-Tmax} is the area under the curve from time zero to the T_{max} for each subject in the 2.0 mg IN study arm.

3.3.4. Pharmacodynamics - Published Literature

The amount of naloxone HCl required to reverse opioid-induced respiratory depression is dependent on the type of opioid requiring reversal as well as the amount of opioid present in the patient. Therefore, reversal of opioid overdose by medical professionals is often empirically determined by repeated dosing of naloxone until a desired degree of respiratory depression reversal is achieved. On the contrary, naloxone HCl products intended for use in the community setting are designed to achieve respiratory depression reversal based on a single dose level because non-medically trained individuals cannot be expected to make medical decisions on dose titration.

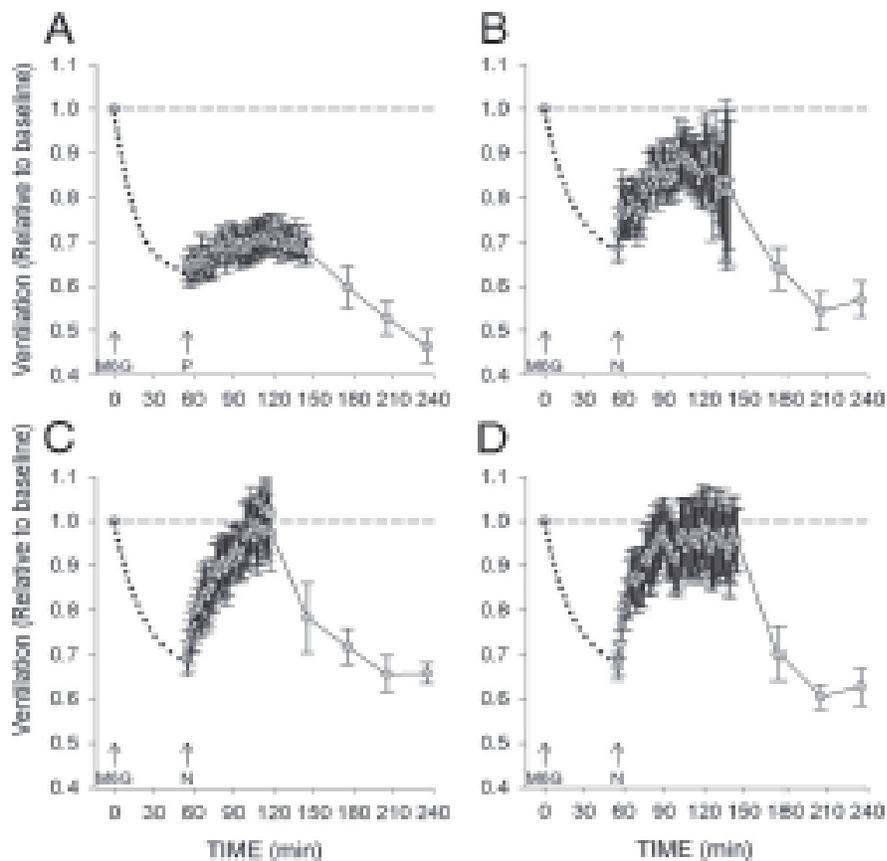
Healthy volunteer studies with naloxone HCl have been conducted in controlled, clinical settings to demonstrate reversal of induced respiratory depression and to explore the duration of naloxone action, the extent of antagonism of various opioids, and adverse effects of naloxone HCl administration (Evans, Hogg, Lunn, & Rosen, 1974) (Amin, et al., 1995) (Gal, 1989) (van Dorp, et al., 2006) (Olofsen, et al., 2010). Intravenous naloxone HCl administration to volunteers (N=6; 5-0.4 mg/70 kg; 1-1.6 mg/70 kg) with severe morphine-induced suppression of ventilatory response leads to well-defined reversal of respiratory depression followed by re-sedation within 45 minutes (Evans, Hogg, Lunn, & Rosen, 1974). In a healthy volunteer study (N=12; 0.006 mg/kg IV bolus) involving continuous infusion with alfentanil or remifentanil, Amin et al. demonstrated that naloxone HCl reversed depressed hypoxic responses without causing clinically significant cardiac changes or adverse events (Amin, et al., 1995). In a placebo-controlled study, Olofsen et al. showed that administration of 0.1 mg or higher naloxone HCl IV to volunteers (N=8/group) who received either morphine or morphine-6-glucuronide (M6G) caused rapid return to baseline ventilation rates followed by renarcotization (see [Figure 10](#) and [Figure 11](#)) (Olofsen, et al., 2010). The duration of reversal was longer for M6G than for morphine, related to the greater potency of naloxone as an antagonist against M6G; higher doses of naloxone HCl extended reversal duration but did not affect speed of reversal.

Figure 10. The Effects of (A) Placebo, (B) 0.2 mg Naloxone HCl, and (C) 0.4 mg Naloxone HCl, 30 Minutes after Administration of Morphine



SOURCE: (Olofsen, et al., 2010)

Figure 11. The Effects of (A) Placebo, (B) 0.025 mg Naloxone HCl, (C) 0.1 mg Naloxone HCl, and (D) 0.4 mg Naloxone HCl, 55 Minutes after Administration of Morphine-6-Glucuronide



SOURCE: (Olofsen, et al., 2010)

Two healthy volunteer studies were conducted to investigate whether a single bolus injection of naloxone HCl would lead to full reversal of respiratory depression when long-acting opioids had been used. Buprenorphine, a long-acting opioid, has a high affinity for opioid receptors and slow receptor association and dissociation as compared with other opioids (Boas & Villiger, 1985). In a placebo-controlled, single-blind study (N=6/group), 5 and 10 mg IV naloxone HCl, but not 1 mg, produced consistent reversal of respiratory depression due to IV buprenorphine, and the reversal was uncharacteristically gradual (Figure 12) (Gal, 1989). In a later study, 2 to 3 mg doses of naloxone HCl followed by 4 mg/hr continuous naloxone HCl IV infusion were shown to lead to full reversal of 0.2 mg buprenorphine (van Dorp, et al., 2006). These findings may be due to more rapid elimination of the bolus dose of naloxone HCl than the long-acting opioid and/or to a high affinity of the long-acting opioid for mu-opioid receptors, resulting in a relative inability to displace the receptor-bound agonist. The difficulty in reversing respiratory depression caused by partial agonists by naloxone HCl is reflected in product labeling and may support development and approval of higher dose naloxone HCl products intended for use in the community setting.

Figure 12. The Effects of Placebo, 1 mg Naloxone HCl, 5 mg Naloxone HCl, and 10 mg Naloxone HCl after Intravenous Administration of Buprenorphine

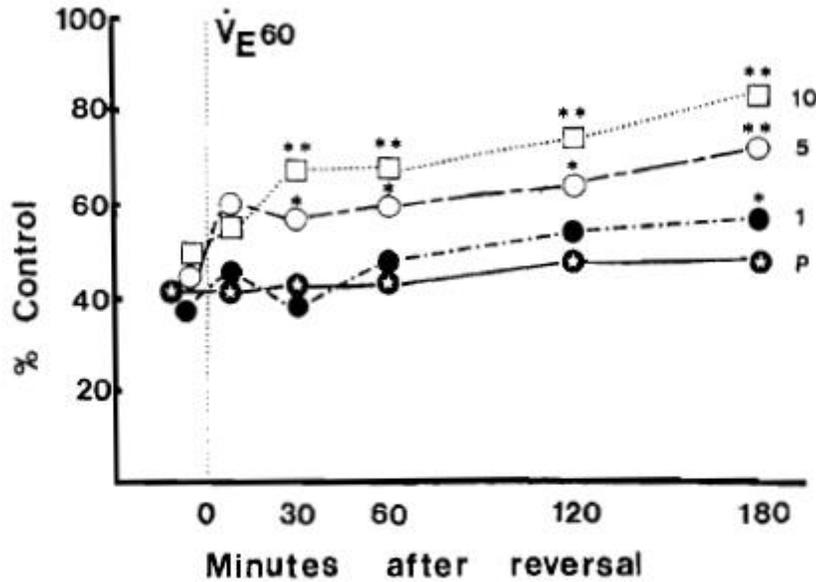


Fig. 3. Changes in minute ventilation at $P_{CO_2} = 60$ mm Hg during rebreathing (\dot{V}_{E60}) after reversal with placebo (P) and 1, 5, and 10 mg naloxone. Mean values are plotted as percent of control. Values before reversal (time 0) are those 2 hours after buprenorphine. * $p < 0.05$; ** $p < 0.01$ denote significant difference from placebo.

SOURCE: (Gal, 1989)

3.4. Data to Support the Device Constituent Component of Naloxone Delivery Products Intended for Use in the Community Setting

The scenario of timely, critical medical intervention by non-medical professionals is not unique to opioid overdose. Emergency-use auto-injectors are available with epinephrine for the treatment of life-threatening anaphylaxis, diazepam for the treatment of refractory seizures, and atropine for the treatment of nerve agent poisoning. Making a safe, effective and easy-to-use naloxone presentation readily available to those at risk for overdose and to those around them who may be in a position to administer this potentially life-saving drug, is analogous to these products; and, considering the epidemic of opioid overdose and related death, is an important endeavor.

To ensure delivery of a safe and effective dose, naloxone HCl products intended for use in the community setting should have the following general characteristics:

- Widely available, FDA approved;
- Usable by non-medical individuals under the stress of an emergency situation (e.g., intuitive use incorporating human factors engineering principles);
- Easily carried (e.g., convenient; portable);
- Ruggedly designed;
- Capable of providing a safe and efficacious dose of naloxone HCl in the community setting;
- Product and labeling to prompt the user to immediately seek definitive emergency medical attention.

3.4.1. EVZIO Product Characteristics

EVZIO is a single-use, self-contained auto-injector that delivers 0.4 mg naloxone HCl via SC or IM injection. The PK of EVZIO 0.4 mg are described in [Section 3.3.2](#). Many of the product characteristics for EVZIO were established by analyzing use scenarios, users, and use environments for administration of naloxone HCl during an opioid overdose emergency.

EVZIO requires no assembly, priming or attachments and is portable by being lightweight and compact (3.4" x 2.0" x 0.64"). Removal of the outer case is the first step to use EVZIO. The durable outer case protects EVZIO and includes a drug viewing window that allows a user to inspect the naloxone drug solution prior to use. The user then pulls off the red safety guard from the black base (the same end as the needle). The black base is placed against the patient's outer thigh and depression of the black base initiates the injection process. The black base cannot be depressed without removing the red safety guard thereby helping prevent unintended activation of EVZIO. The injection process is powered by the release of compressed gas from within a gas cylinder inside of the device. After the naloxone dose is delivered, the gas is vented, allowing a retraction spring to decompress and retract the needle back up into the housing of EVZIO. The user does not see the needle before, during, or after use. An illustration of EVZIO is in [Figure 13](#).

Figure 13. Illustration of EVZIO, EVZIO Outer Case, and a Used EVZIO



SOURCE: EVZIO INSTRUCTIONS FOR USE; APRIL 2014

EVZIO is designed to provide multiple cues to help aid the user. In addition to labels on each auto-injector that provide written and pictorial instructions for use, EVZIO includes an electronic prompt system that is activated with the removal of the outer case and provides audible instructions for use and visual cues (red and green blinking lights) to assist in guiding the user through the injection process.

The electronic prompt system is independent from the naloxone delivery functionality (i.e., the drug delivery functionality of the device will still work even if the audio/visual prompts do not work). These labeling and electronic prompt systems were evaluated in Human Factors studies and have reproducibly demonstrated that untrained users without access to instructional leaflets can successfully use EVZIO >90% in a simulated emergency use scenario.

In addition to containing 2 EVZIO devices, each carton of EVZIO includes a Trainer for EVZIO (Figure 14) that works the same way as EVZIO except that it does not contain a needle or medicine. Just like EVZIO, the Trainer for EVZIO has an electronic voice instruction system and blinking red and green lights to help guide the user through the injection process. The Trainer for EVZIO can be reused so users can practice giving an injection before an opioid emergency occurs. The Trainer Instructions for Use (IFU) leaflet explains in text and pictures how to use the Trainer. A Patient Information Leaflet (PIL), with clear written and pictorial instructions for use, is also included with each EVZIO prescription. The Trainer for EVZIO and the PIL help support the use of EVZIO in community settings by non-medical personnel.

Figure 14. Illustration of a Trainer for EVZIO



SOURCE: TRAINER FOR EVZIO INSTRUCTIONS FOR USE; APRIL 2014

3.4.2. EVZIO Sharps Injury Prevention Feature

EVZIO contains a sharps injury prevention feature in the form of a retractable needle. The needle is not visible to the user before, during, or after the injection. After the needle retracts into the housing, the black base is locked and the needle cannot exit the housing. The retractable needle safety system minimizes exposure of the needle in the body as well as protects the user from inadvertent needle exposure and associated infectious disease transmission by preventing finger/digit access to the needle and other bodily fluid exposure before and after an injection. In the sharps injury study, all 500 tested auto-injector devices worked as intended, puncturing an orange and retracting within 5 seconds, providing a 95% confidence interval that the device failure rate is less than 1%.

3.4.3. EVZIO Features that Aid the User after Administering a Dose

EVZIO includes several visual and auditory signals to confirm successful delivery of a dose. First, the viewing window that shows the drug solution becomes blocked by a red indicator after the drug has been expelled through the needle. Second, the black base becomes locked and no longer functions. Third, the electronic prompt system features a 5 second countdown and instructs the user “injection complete. Seek emergency medical attention” and the LED on the front of the device blinks red. Dose confirmation and post-use instructions to seek emergency medical care are important features for emergency use products intended for use by laypersons in the community.

3.4.4. In vitro Performance Testing of EVZIO for “Real Word” Use

EVZIO was tested according to a verification and validation test plan, and included testing associated with the following well-known industry requirements: ISO 11608-1:2012, ISO 11608-2:2012, and ISO 11608-3:2012, IEC 60601-1, UL, ASTM, and ISTA. Tests were incorporated to ensure traceability to risk analyses, including design and manufacturing risk analysis, and Human Factors and Use Error Analysis. These risk analyses were conducted in accordance with ISO 14971:2007 Medical Devices - Application of risk management to medical

devices. In addition, consideration was made in developing the test program by reviewing the FDA Guidance on Injectors.

Importantly, EVZIO was tested to ensure that it would deliver an accurate dose under “real world” situations including:

- Injection through material to simulate a seam of clothing such as jeans;
- Accelerated Aging to ensure the device constituent components will function over the shelf life of the product;
- Environmental conditions ranging from 5°C through 40°C;
- Testing at an altitude of 10,000 feet elevation;
- Pre-conditional testing such as after a drop of a minimum of 1 meter, or after vibration, or after exposure of dry heat, or after exposure to cold storage;
- Testing to demonstrate the device could withstand 300 pounds of force;
- Testing after chemical exposure such as window cleaner, soap, bleach, acetone, nail polish, hand sanitizer, stain remover, and hydrogen peroxide; and
- Testing to ensure simulated rain would not penetrate the device.

3.4.5. Human Factors Studies for EVZIO

3.4.5.1. Formative Studies

Multiple formative studies were conducted that serve as the foundation for the user interface development of EVZIO and inform on design features including IFU and electronic prompts for key tasks (i.e., case removal, safety guard removal, and base activation). A formative user needs evaluation study using a prototype containing no needle or drug, was conducted in individuals caring for someone taking opioid medication (Study IJ-1000FE-03O); and led to changes in text and symbols and a decision to include a Trainer device with every prescription to ensure proper training. The subsequent formative usability and label evaluation study enrolled patients currently taking opioid medications and caregivers (Study IJ-1001FE-03O). Participants were asked to simulate an injection into a mannequin using different device labeling configurations. All participants completed the simulated injection successfully suggesting that the PIL and instructions on the device were effective and facilitated correct use of EVZIO. The results of the study provided evidence that EVZIO was ready for user interface design validation testing.

3.4.5.2. Summative Design Validation Study – Intuitive to Use Without Training

A Summative Design Validation Study to validate the user interface of EVZIO was also conducted (IJ-1025SE-03O). This was an open-label study to evaluate participants’ ability to correctly give an injection into an adult-sized mannequin using an EVZIO Study Device (no needle or drug) during a simulated opioid overdose scenario without training or reading the PIL that includes the IFU. The testing environment included variables aimed at inducing stress (e.g., beeping timer that increases in frequency and loudness, multiple evaluators, confined testing space).

Forty participants (20 juveniles, aged 12-19, and 20 adults, aged 20-65) completed the study, and results showed that EVZIO was used successfully by untrained juveniles and adults to deliver a simulated dose of naloxone based on only the device label and voice and visual prompts. Thirty-six (36) out of 40 participants (90%) delivered a simulated dose of naloxone. The average time to complete the simulated injection from selection of EVZIO to injection completion was approximately one minute. Of the 40 participants, 28 (70%) rated all steps of the injection as “Easy” or “Very Easy.”

3.4.5.3. *Relative Usability of EVZIO Compared to the Off-Label Intranasal Naloxone Kit*

Two Human Factors studies to compare the usability of EVZIO and an off-label IN Naloxone Kit were conducted (Studies IJ-1026SE-03O and IJ-1027SE-03O). The studies, conducted at two different facilities using the exact same study design and analysis plan, compared the participants’ ability to successfully use the naloxone delivery devices before and after focused training. In Phase 1, participants had to rely on the provided instructions for the off-label IN Naloxone Kit (leaflet used in Harm Reduction Center training) and the EVZIO device labeling/voice prompts (no instructions for use leaflets) in order to successfully use the devices in a simulated opioid emergency use scenario. In Phase 2, conducted on the same day as Phase 1, a nurse provided a one-on-one 30-minute training session on each device to instruct the participants on proper use. Lastly, in Phase 3, conducted at least 7 days after Phase 2, participants had to use each naloxone delivery device again in a simulated emergency use scenario without any additional instructions or training.

Results from both studies are presented in [Table 6](#) and show that untrained users can successfully administer a dose of naloxone using EVZIO with a success rate >90% during a simulated opioid emergency. After training (in Phase 3), users successfully administer a dose of naloxone using EVZIO with a success rate of 100%. In post-test interviews, the majority of participants (>98%) said that EVZIO was easy to use, largely due to EVZIO’s voice instructions, and >92% of participants stated they would feel confident using EVZIO in an actual emergency. The results for the off-label IN Naloxone Kit indicate that a large percentage of participants had difficulty successfully administering a dose of naloxone even after training was completed.

Table 6. Summary of Successful Critical Task Completion in Two Controlled Usability Studies

	Study IJ-1026SE-03O		Study IJ-1027SE-03O	
Number of Participants	42		41	
Successfully Completed Critical Tasks ¹ , n (%)	Phase 1	Phase 3	Phase 1	Phase 3
EVZIO	38 (90.5%)	42 (100%)	40 (97.6%)	41 (100%)
Off-label Naloxone IN Kit	0 (0%)	24 (57.1%)	0 (0%)	18 (43.9%)

¹ Critical tasks were defined as whether or not the simulated patient would have received a potentially life-saving dose of naloxone had the scenario been an actual opioid overdose emergency.

4. DISCUSSION AND CONCLUSIONS

The purpose of this section is to summarize relevant information to support the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee in their discussion of naloxone HCl products intended for use in the community, specifically the most appropriate dose or doses of naloxone HCl to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in this setting.

Two naloxone HCl products have been approved by the FDA in all patient populations for use in the community setting: EVZIO (naloxone HCl injection, USP) 0.4 mg auto-injector; and NARCAN (naloxone HCl) Nasal Spray 4 mg. Both products are provided in a carton with two units so that a second dose is available in case the desired response is not observed following the first dose. A third product that is commonly used in the community setting is a naloxone HCl injection, USP luer-lock prefilled syringe fitted with a nasal atomizer for IN administration (off-label IN Naloxone Kit).

Safety of Naloxone HCl Products

Naloxone HCl injection has been used for over 40 years to reverse the effects of opioids and is widely considered a safe drug. Doses well above the FDA labeled initial dose have been administered without significant adverse effects. Risks associated with naloxone HCl are well-documented in the literature and in the prescribing information of marketed naloxone HCl products. Naloxone HCl has essentially no effect in individuals not exposed to an opioid, therefore there is little safety risk associated with accidental use of naloxone HCl in someone who isn't suffering from opioid-induced respiratory depression. The most frequent adverse reaction associated with the use of naloxone HCl is precipitated acute withdrawal syndrome in opioid-dependent individuals, which can be life-threatening in neonates. Other serious adverse effects of naloxone HCl include cardiovascular effects, though it is unclear whether these adverse effects are caused directly by naloxone HCl, secondary to hypoxemia from the opioid intoxication, or as part of an acute withdrawal syndrome induced by naloxone HCl administration.

Post-marketing safety results for EVZIO further support the safety profile of naloxone HCl use in the community setting. Between July 2014 and April 2016, a total of 275,527 EVZIO auto-injectors were distributed. The number of adverse events (N=15) for EVZIO during this time frame is small.

Pharmacokinetics of Naloxone HCl in Humans

The relative bioavailability of 0.4 mg naloxone HCl administered IM/SC to the anterolateral thigh using EVZIO compared to a standard syringe has been established in a study of 30 healthy subjects. EVZIO provides equivalent naloxone AUC and 15% greater naloxone C_{max} in comparison to a single 0.4 mg IM/SC naloxone HCl injection administered using a standard syringe.

The relative bioavailability of NARCAN Nasal Spray to naloxone HCl administered into the *gluteus maximus* muscle using a standard syringe has been established in a study of 30 healthy subjects. 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 HCl administered by IM injection was 46.7%, and 43.9%, respectively. However, in a PK study of 36 volunteers with chronic rhinitis the relative bioavailability of 2.0 mg naloxone HCl administered IN using the off-label IN Naloxone Kit compared to the same dose administered IM using a standard syringe to the anterolateral thigh resulted in a much lower relative bioavailability of approximately 14.6%. The inconsistency in relative bioavailability results for NARCAN and the IN Naloxone Kit may be due to differences in the patient populations studied, location of the IM injection, formulation, IN device delivery performance, or a combination of these factors.

It has been suggested in the literature that abnormal nasal physiology, drug interactions and certain diseases may impact the absorption and bioavailability of drugs administered IN, including naloxone HCl. In a PK study of 36 volunteers with chronic rhinitis, the relative bioavailability of 2.0 mg naloxone HCl administered using an IN Naloxone Kit in the presence and absence of pre-treatment with oxymetazoline HCl 0.05% nasal solution USP (Afrin®, Merck & Co., Inc.) was compared (Study IJ 901DV 03O). The bioavailability of naloxone HCl administered IN after oxymetazoline was lower than naloxone HCl administered IN as monotherapy with geometric mean ratios (IN+ oxymetazoline / IN) for C_{max} and both AUC_{0-t} and AUC_{0-inf}. The absorption was most prominently impacted during the first hour of absorption. The results from this study demonstrate that administration of a commonly used over-the-counter vasoconstrictor, oxymetazoline, 30 minutes prior to IN naloxone HCl administration had a striking reduction in naloxone plasma concentrations. Sponsors of IN naloxone HCl products should consider evaluating these possible interactions with their products to better inform prescribers and patients of any potential risks.

Selection of Appropriate Doses/Dose Algorithms

To address the opioid epidemic, FDA has encouraged the development of naloxone HCl products for use in the community setting using routes of administration easily performed by a non-medical professional. Selection of 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 is complex. Due to differences in relative bioavailability between routes of administration, the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages should be decided separately based on route of administration and clearly explained in the product labeling. The most appropriate dose or doses would apply to all naloxone HCl products within the route of administration.

The most appropriate dose or doses for a given route of administration should provide the best risk/benefit profile for their intended use. Repeat dosing instructions (dosing algorithm) should be easily understood by prescribers, patients and caregivers. Avoiding confusion is critical to ensuring naloxone HCl is administered quickly during an opioid emergency. A dose algorithm that addresses the majority of potential treatment needs within the community (e.g., ages, opioids, dose of opioids, etc.) would reduce the potential for confusion (e.g., failure or delay to

administer naloxone HCl). Rare treatment needs (e.g., opioid-dependent neonates) that are not fully addressed by a dose algorithm may best be addressed in the labeling to avoid confusion.

Additional Considerations for Naloxone HCl Products used in the Community Setting

To ensure delivery of a safe and effective dose, all naloxone HCl products intended for use in the community setting should have the following general features:

- Widely available, FDA approved;
- Usable by non-medical individuals under the stress of an emergency situation (e.g., intuitive use incorporating human factors engineering principles);
- Easily carried (e.g., convenient; portable);
- Ruggedly designed;
- Capable of providing a safe and efficacious dose of naloxone HCl in the community setting;
- Product and labeling to prompt the user to immediately seek definitive emergency medical attention.

Products intended for use in the community setting need to be designed and tested to prove that they are robust, reliable and intuitive to use by non-trained individuals in an emergency situation. A product that contains a life-saving medication poses significant risk to patients if it cannot be used as directed by the intended user population in the intended setting.

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Advisory Committee Briefing Materials: Available for Public Release

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

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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/m^2). 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)*].

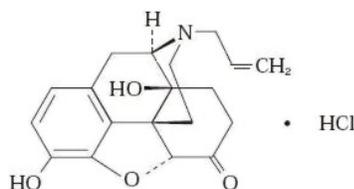
8.5 Geriatric Use

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 (\pm SD) C_{max} value of 1.24 (\pm 0.64) ng/mL. The mean (\pm SD) plasma half-life of naloxone in healthy adults was 1.28 (\pm 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 (\pm SD) C_{max} value was 1.07 (\pm 0.48) ng/mL. The mean (\pm SD) plasma half-life was 1.36 (\pm 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

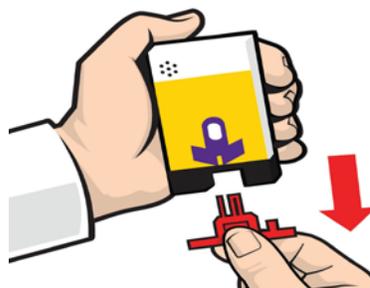


Do not go to Step 2 (Do not remove the **Red** safety guard.) until you are ready to use EVZIO. **If you are not ready to use EVZIO, put it back in the outer case for later use.**

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.

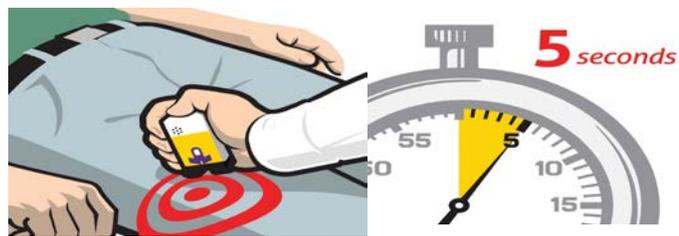
Note: The **Red** safety guard is made to fit tightly. **Pull firmly to remove.**

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

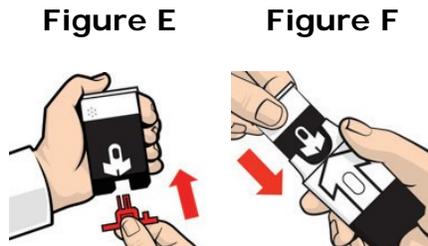


Only practice using the middle of the outer thigh. The outer thigh is where you would inject with the real EVZIO.

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



Opioid Emergencies

+

**Life-threatening
Respiratory Depression**

Helping Address a Growing
Public Health Threat



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1 The Opioid Benefit-Risk Continuum

+ Pain recognized as the fifth vital sign in 1996.

+ Opioids are the mainstay of chronic pain treatment for chronic non-cancer pain.

+ Opioid risk and benefit is a clinical decision based on efficacy and side effect profiles that include: nausea, vomiting, sedation, dizziness as well as the most serious side effect of respiratory depression.

+ The threshold for toxicity and overdose levels varies from patient to patient, causing the therapeutic and toxic doses of opioids to potentially overlap.

Opioids have been used for thousands of years to treat acute and chronic pain.¹ After recognizing pain was undertreated in this country, the medical community proposed pain as the fifth vital sign in 1996 and prescriptions for opioid analgesics increased seven fold over the next four years.² Opioids are now a mainstay of medical therapy used by millions of patients each year driven primarily by chronic opioid treatment (COT) of chronic non-cancer pain (CNCP).

Opioids bind to μ -opioid receptors in the central and peripheral nervous system in an agonist manner to elicit analgesia.¹ As with most medical therapies, benefits and risks must be weighed to determine appropriate use in individual patient therapy decision-making. A major benefit for prescribing opioids is for pain management in acute and chronic settings as well as with cancer-related

symptomology.³ Other benefits of opioids are for cough suppression and in the treatment of opioid dependence associated with an opioid use disorder.⁴ Adverse effects of opioids include constipation, nausea, vomiting, sedation, dizziness, physical dependence, and tolerance.⁵ However, respiratory depression is the most important serious adverse effect of opioids as it can be immediately life-threatening.⁶ This guide is meant to serve as a resource for understanding the epidemiology, pathophysiology, risk factors and treatment of opioid emergencies characterized by life-threatening respiratory depression. Specific information is included on the role of opioid antagonists such as naloxone in managing life-threatening opioid-induced respiratory depression (OIRD).

Opioid Overdose: A Misnomer

Overdose is defined as “an excessive dose” or use of a drug resulting in adverse reactions ranging from mania or hysteria to coma or death. In the context of opioids, the term “overdose” when applied universally to anyone who has suffered from morbidity or mortality attributed to opioids may be a misnomer as it implies that one either intentionally took more opioid than prescribed (e.g. through abuse or misuse) or unintentionally consumed an excessive dose that was not prescribed (e.g. children suffering from accidental opioid exposure). However, this generalization does not take into account the physiological changes that can produce manifestations of life-threatening respiratory depression even at therapeutic opioid levels.

A very important consideration when treating patients with opioids is that the therapeutic window is narrow and may vary between different opioids. The threshold for toxicity and overdose levels varies from patient to patient, causing the therapeutic and toxic doses of opioids to

The threshold for toxicity and overdose levels varies from patient to patient, causing the therapeutic and toxic doses of opioids to overlap.

Respiratory depression is the most important serious adverse effect of opioids as it can be immediately life-threatening.

- FDA 2014

overlap. The risk of an opioid emergency continues beyond the therapeutic and clinical duration of action for most opioids.⁷

Therefore, if an individual being treated with chronic opioid therapy undergoes a change that lowers the toxicity threshold, or increases the level of opioid in the blood system such that opioid levels cross the toxicity threshold, then that patient can experience an opioid emergency at an opioid dose that was considered safe and not “an excessive dose” previously. The most concerning side effect subject to resultant threshold changes due to incomplete tolerance is opioid-induced respiratory depression (OIRD) and potential for life-threatening hypoxia and apnea.

::: FIGURE 1



~3,300 children

On average, ~3,300 children \leq 5 years old suffer unintentional opioid exposure or poisoning each year.

2 Opioid Emergencies in the United States

+ Opioid-related drug poisonings represent a large and growing epidemic in the United States for both morbidity and mortality.

+ In 2014, of 47,055 deaths from drug poisoning, 18,893 were attributed to opioid analgesics, representing 40% of drug poisoning deaths.

The Centers for Disease Control and Prevention (CDC) injury data reveal that drug poisoning is the number one cause of injury death in the U.S. Prescription opioids are responsible for more than a third of those deaths. Death rates, sales of prescription opioids and substance abuse treatment admissions increased congruently from 1999-2008.⁸ The total number of deaths from drug poisoning surpassed traffic collisions in 2009 as the leading cause of unintentional injury deaths in the United States, driven mostly by prescription opioids.^{9,10} The age group that is at the highest risk for drug overdose is 45-54 years of age. In 2013, unintentional poisoning was the number one cause of death for 45-54 year olds and the total deaths were approximately 10,000 whereas the number 2 cause (motor vehicle collisions) were approximately 5,000.¹¹

Opioid-related drug poisoning deaths represent a large and growing epidemic in the United States.

+ On average, there are roughly 136,000 emergency room visits due to prescription opioid overdose and opioid-induced respiratory depression (OIRD) every year.

+ Over 50% of emergency room visits for opioid overdose and OIRD result in admission/hospitalization.

Mortality rates for opioid overdose have been on the rise. Although the rate of increase per 100,000 population has slowed since 2006, the total number of annual fatalities from prescription opioids quadrupled from 1999-2010 and plateaued over the next three years at levels over 16,000.¹²⁻¹⁵ However, during that same timeframe, deaths from heroin increased 2.7 times from 3,000 to over 8,200.¹⁶ In 2013, of 43,982 deaths from drug poisoning, 16,235 were attributed to opioid



of all drug poisoning deaths are attributed to opioids.

On average, there are roughly 136,000 emergency room visits due to opioid overdose and OIRD every year.

analgesics, representing 37% of drug poisoning deaths.¹³ Of the fatalities relating to opioids, 60% occur in persons seeing a single doctor and 83% are unintentional, equivalent to 44 fatalities every day.^{16,17} Recently, early 2014 mortality data has been released demonstrating deaths involving opioid analgesics and heroin spiked 14% compared to 2013 (28,647 deaths), 18,893 (a 16% increase) involved prescription opioids and 10,574 (a 28% increase) involved heroin.¹⁸ Prescription opioid-related deaths increased in part due to a 79% increase in deaths involving synthetic opioids, such as fentanyl and tramadol.¹⁹

Accidental opioid emergencies, including overdose, are not uncommon among patients taking opioids prescribed for an underlying medical condition. For example, in a large retrospective Veterans Health Administration study, 73% of patients having a life-threatening opioid-related respiratory depression event were prescribed an opioid for a medical condition such as chronic pain and did not have a previous diagnosis of a substance use disorder.²⁰

There has been much discussion surrounding opioid-related death in the country; however, the morbidity of this disease is perhaps even more

startling. On average, there are roughly 136,000 emergency room visits due to opioid overdose and opioid-induced respiratory depression (OIRD) every year.²¹ Over 50% of emergency room visits for opioid overdose and OIRD result in admission/hospitalization.²² The average length of stay in an inpatient setting is about 3.6 days, with an average charge of \$30,000 or greater per patient per visit.^{23,21} Up to 10% of emergency room visits for opioid overdose and OIRD result in near-fatal events requiring advanced supportive measures, including admission to the Intensive Care Unit and mechanical ventilation.²⁴ Additionally, many patients admitted for an opioid emergency are not discharged home. Rather, studies show that up to 22% are discharged to another institution such as a nursing home or rehabilitation center following their emergency room stay and admission.²³

Deaths involving opioids increased 14% in 2014 compared to 2013.

::: FIGURE 2



83%

of fatalities relating to opioids are **unintentional**,
equivalent to **44 fatalities** every day.

3 Pathophysiology of Opioid-induced Respiratory Depression

+ Opioids produce activity through three different receptors; Mu (μ), Kappa (κ) and Delta (δ).

+ Opioids that have agonist activity at either μ or δ receptors can lead to respiratory depression.

+ The effects of exogenous opioids on respiration include changes in both tidal volume and respiratory frequency. The nature of the effect depends in part on the concentration of the opioid.

+ μ -opioid agonists affect chemosensitivity by blunting central chemosensitivity to hypercapnia and hypoxia, contributing to life-threatening respiratory depression.

+ Special considerations relating to opioid effects include tolerance, use of partial agonists, opioid metabolism (CYP3A4 or 2D6 polymorphism), and the lipophilicity of opioid preparations.

Opioids produce activity through three different receptors:



Most opioids produce activity at μ -receptors (e.g., morphine, methadone and fentanyl). Opioids that have agonist activity at either μ or δ receptors cause respiratory depression. κ -receptor agonists produce either no effect on respiration or cause a mild respiratory stimulation and do not produce the euphoric and reinforcing effect of μ agonist opioids while δ -receptor agonists seem to have some reinforcing properties.²⁵

Under normal circumstances, carbon dioxide (CO_2) levels in the blood stimulate a person's respiratory drive. As breathing slows down, CO_2 levels increase, which stimulates the brainstem to increase the respiratory rate. When an individual accumulates opioid levels above the therapeutic window, the high levels of opioids bound to receptors will decrease alertness and induce sleep. During sleep, it is the built-in CO_2 feedback loop that maintains respiratory drive, but when blocked by opioid levels, respiration is impeded, including a decrease in tidal volume and rate which can lead to apnea.²⁶

Abdominal rigidity due to high-dose opiates along with decreased phrenic nerve and diaphragmatic muscle activity also reduces tidal volume and minute ventilation. Other affects of opioids on the chest and lungs include decreased chest wall

compliance, increased pulmonary resistance, vocal fold closure and pharyngeal airflow obstruction.²⁷

Because opioids depress a patient's respiratory drive, mild to moderate OIRD is a common and expected side effect, along with many of the adverse effects listed above.²⁸ Life-threatening OIRD, when present, will result in hypoxemia, causing brain injury from apnea, which eventually leads to cardiac dysrhythmias, cardiac arrest and death.²⁹ In summary, μ -opioid agonists blunt central chemosensitivity to hypercapnia and hypoxia, contributing to life-threatening respiratory depression.²⁷

Neuroanatomy and neurophysiology of OIRD

Opioids contribute to unconsciousness by binding to opioid receptors in the periaqueductal gray, medulla and spinal cord to reduce nociceptive transmission.²⁷ The pre-Bötzinger complex, located within the ventrolateral medulla, is now believed to be the crucial site of action of opioids in respiratory depression. There are inspiratory, expiratory and non-respiratory neurons within the pre-Bötzinger complex, with a sub-population of these neurons expressing neurokinin-1 receptors (NK1R). Most of the NK1R-expressing pre-Bötzinger neurons are active during inspiration, and are preferentially inhibited by opioids. These NK1R-expressing neurons within the pre-Bötzinger complex are the critical sites in mediating OIRD. Opioid exposure to the pre-Bötzinger region expressing NK1R caused NK1R inhibition and results in respiratory rhythm arrest, abolished muscle activity and fatal apnea.²⁷

A secondary feedback modulatory mechanism affecting respiration, the Kölliker-Fuse (KF)

nucleus and parabrachial complexes in the dorso-lateral and ventrolateral pons produce irregular respiratory patterns when stimulated by μ -opioid agonists.²⁷ Additionally, decreased awareness of respiration through dampening of the response to hypercapnia has been found to occur through decreasing activity in the bilateral insula and operculum. Finally, opioids indirectly depress breathing by inhibiting brainstem arousal centers. This occurs by inhibiting acetylcholine release in the medial pontine reticular formation.

Special Considerations

Tolerance

Long-term exposure to opioids can produce tolerance to the opioid effects. Tolerance is a loss of analgesic potency leading to the patient requiring escalating doses and exhibiting decreasing analgesic effectiveness over time.⁵ Types of acquired tolerance are (i) pharmacokinetic—changes in metabolism; (ii) pharmacodynamic—changes in receptor-signal transduction pathways; and (3) learned tolerance—decreased efficacy as compensatory mechanisms are incorporated or learned.^{5,30,31} Tolerance to all the effects of certain opioids is not equal. It is frequently assumed that there will be no adverse effect of higher doses on respiratory function in patients taking chronic opioids because the rate of development of tolerance will be similar for the respiratory depressant effects as it is to the development of tolerance of other opioid effects. However, tolerance to the respiratory depressant effects of opioids is not equivalent to analgesic tolerance nor is it complete, and, as a result, long-term opioid users remain at significant risk for life-threatening respiratory depression. For

example, in two human studies involving the opioid methadone, differentiated tolerance between CO₂ chemoreceptors was found to be complete whereas tolerance to hypoxia-sensitive chemoreceptors was found to be incomplete.²⁵

Partial Agonists

Because OIRD arises from the stimulation of μ -opioid receptors (MORs), which control not only analgesic effects but also breathing, the receptor selectivity of a given opioid influences resultant respiratory effects.³² Most of the commonly used opioids are full MOR agonists, whereas others such as buprenorphine, butorphanol, pentazocine, and tramadol are opioid partial and/or mixed agonists, thereby lowering (although not eliminating) the risk of respiratory depression compared with full agonists.

For example, reversal of life-threatening OIRD caused by the partial opioid agonist buprenorphine has presented unique challenges stemming from its opioid-binding characteristics.^{33,34} Naloxone resistance has been postulated for buprenorphine because of its extremely high μ -receptor binding affinity, but there is evidence to support the idea that full reversal may be possible depending on

Partial agonist receptor binding presents challenges for reversing life-threatening OIRD.

Long-term opioid users remain at significant risk for life-threatening respiratory depression.

the dosing of both agents.³³ In a subsequent study, the pharmacodynamics between naloxone and buprenorphine was assessed in healthy volunteers.³⁴ In light of slow receptor association/disassociation kinetics of buprenorphine coupled with fast elimination kinetics of naloxone, it was concluded that administering naloxone via continuous IV infusion may be most efficacious in this setting.

Opioid Metabolism and Impact on OIRD

Structural differences across the various opioids also translate into differences in metabolism, which in turn contribute to variable efficacy and safety in a given patient and in certain populations.³⁵ For some agents, phase 1 metabolism occurs by CYP2D6 (codeine, hydrocodone, oxycodone) to an active metabolite, the latter 2 by CYP3A4 to inactive metabolites, fentanyl by CYP3A4 to inactive metabolites, whereas others are metabolized to some extent by several pathways, such as tramadol by 2D6 (to active metabolite) and 2B6, 3A4 to 5 metabolites total. Methadone metabolism is perhaps the most complex; it involves at least 6 CYP pathways but is primarily mediated by CYP3A4 and CYP2B6. Morphine, hydromorphone, levorphanol, oxymorphone, and tapentadol

undergo phase 2 metabolism by glucuronidation via UGT2B7, which also affects the metabolism of the hydromorphone and oxycodone, which are active metabolites of hydrocodone and oxycodone, respectively. Metabolism rates also vary from person to person because of polymorphic variants among various populations.³⁶

Variance in individual metabolism of opioids puts some individuals at a greater risk of life-threatening OIRD. For example, 1-7% of Caucasians and greater than 25% of Ethiopians have gene duplications of the gene which encodes for the cytochrome P450 enzyme CYP2D6 and metabolize opioids at a greatly increased rate. Conversely, 7- 10% of the Caucasian population have no functional CYP2D6 alleles and are therefore poor metabolizers. Patients with increased metabolism of opioids run a greater risk of respiratory depression than poor metabolizers.²⁷

Lipophilicity

Lipophilicity is another key consideration in assessing the duration of action of opioids, producing prolonged activity and potential side effects.³⁷ Highly lipophilic examples include fentanyl and sufentanil, whereas poorly lipophilic examples include morphine, meperidine, and hydromorphone. Fentanyl patches and transmucosal immediate-release formulations, due to their lipophilic properties, carry substantial potential for deliberate abuse and overdose, as well as accidental overdose and resultant death.³⁸

Variance in individual metabolism of opioids puts some individuals at a greater risk of life-threatening OIRD.

::: FIGURE 3



4 Patient Populations at Increased Risk for Life-threatening OIRD

+ Identification of patients at greatest risk for life-threatening OIRD has been validated in two databases, one in the VHA population and one in a larger commercial database to evaluate the factors that lead to the highest risk of serious or life-threatening OIRD.

+ Variables identified by the case matched controls were used to develop a Risk Index for Overdose or Serious prescription Opioid-induced Respiratory Depression (RIOSORD).

+ RIOSORD is the first known screening questionnaire developed to provide real-time, evidence-based information to the healthcare professional regarding the risk of overdose or serious respiratory depression in medical users of prescription opioids and is currently being piloted in the VA Healthcare System.

From a macro-level, there are four distinct population groups who are opioid users at risk for life-threatening OIRD and overdose: (i) patients with an opioid prescription who are prescribed and using an opioid for the treatment of a medical condition such as pain, (ii) patients with a prescription for an opioid who are using opioids for non-medical reasons, (iii) individuals using opioids without a prescription non-medically (e.g. accessing opioids through diversion), and (iv) illicit opioid users (i.e. heroin users).³⁹

Analysis of Risk Factors for OIRD in United States Veterans

A retrospective, nested, case-control analysis of Veterans Health Administration (VHA) administrative claims data was completed to assess factors associated with serious opioid-related toxicity and overdose in medical users of prescription opioids. 817 cases of life-threatening

opioid-related respiratory and CNS depression or overdose were identified in the population. Ten controls were randomly assigned to each case. Logistic regression was used to examine associations with the outcome.

The strongest associations included a maximum prescribed morphine equivalent daily dose (MEDD) ≥ 100 mg, history of opioid dependence and hospitalization during the 6 months before the study-identified opioid emergency. Demographic variables confirmed in the present study were non-Hispanic white race, never married and widowed marital status and residence in the Western United States. Most case patients were aged 55 years or older (which is more reflective of the VHA population as compared to the general population). There was a strong association of serious OIRD or overdose and mental health disorders (bipolar disorders). Abuse of alcohol, illicit opioids and other substances is more frequent among medical

users of prescription opioids than in the general population or among chronic pain patients not treated with opioids. Polypharmacy was observed with psychoactive drugs commonly prescribed for mental health disorders such as benzodiazepines, antidepressants, and antipsychotics, as well as mental illness itself, was involved in approximately 50% of overdose events. Hepatic, renal and pulmonary diseases were comorbidities associated with increased risk. Opioid-specific factors associated with increased risk included use of extended release and long acting opioids as well as MEDD ≥ 20 mg.²⁰

Analysis of Risk Factors for OIRD in the United States

In a subsequent study, a US database of integrated commercial health plan claims information was used to assess a larger and more representative population of medical users of prescription opioids for risk factors associated with overdose or serious prescription opioid-induced respiratory depression (OSORD). Among the approximate 18 million patients with an opioid claim during the baseline period, 7,234 case patients were identified who experienced an OSORD event and were matched with 28,932 controls. The covariates most strongly associated with experiencing OSORD in this large integrated commercial population included 8 co-existing health conditions (neuropsychiatric disorders and impaired drug metabolism or excretion) and 8 prescription drug factors (specific opioid drug characteristics and concomitant benzodiazepines or antidepressants). The model had a C-statistic of 0.90, indicating excellent discrimination between cases and controls. Table 1 includes the variables demonstrating significance.

The variables were then used to develop a Risk Index for Overdose or Serious prescription Opioid-

Patients taking opioids with certain comorbidities, concomitant medications or opioid-related factors are at increased risk for life-threatening OIRD and overdose.

induced Respiratory Depression (RIOSORD) with the goal of balancing the scientific and statistical robustness of each included factor's association with OSORD against the practical need for a relatively brief questionnaire with optimum simplicity and accuracy when completed by a healthcare professional in the context of a typical busy community care setting. From the RIOSORD, a predicted probability of an OSORD event within the next 6 months was extrapolated into 7 risk classes, with the average predicted probability ranging from 2% in the lowest risk class to 83% in the highest. Predicted and observed occurrence of an event increased commensurately.⁴⁰

RIOSORD is the first known screening questionnaire developed to provide real-time, evidence-based information to the healthcare professional regarding the risk of overdose or serious respiratory depression in medical users of prescription opioids. RIOSORD performed well in identifying the

**TABLE 1: Multivariable Logistic Regression Model:
RIOSORD Covariates**

Covariate (During 6-month Baseline Period)	Odds Ratio (95% Confidence Limits)
DEMOGRAPHICS	
Age Category 55+ vs 18-34	1.16 (1.04, 1.29)
Patient region Midwest vs Northeast	1.2 (1.08, 1.33)
Patient region West vs Northeast	1.39 (1.23, 1.58)
PRESCRIPTION DRUG USE	
Opioid Drugs By Active Ingredient	
Hydrocodone	1.3 (1.2, 1.41)
Oxycodone	1.5 (1.38, 1.64)
Tramadol	1.19 (1.08, 1.31)
Fentanyl	3.72 (3.1, 4.46)
Morphine	2.93 (2.49, 3.43)
Hydromorphone	2.04 (1.69, 2.45)
Methadone	2.8 (2.22, 3.51)
By Formulation (Non ER/LA Reference)	
ER/LA	1.73 (1.51, 1.99)
By Route Oral (Non-Oral Reference)	
Max Prescribed Daily MED ≥ 100	2.04 (1.87, 2.24)
COMORBIDITIES	
Charlson Comorbidity Index (CCI)	
Congestive Heart Failure	2.06 (1.74, 2.44)
Cerebrovascular Disease	2.52 (2.18, 2.92)
Chronic Pulmonary Disease	1.72 (1.56, 1.89)
Serious Autoimmune Rheumatologic Disease	1.47 (1.23, 1.77)
Chronic Renal Disease	2.17 (1.83, 2.57)
Skin Ulcers	1.5 (1.18, 1.9)
Other Selected Pain and Non-Pain Comorbidities	
Substance Use Disorder	12.74 (11.46, 14.16)
Non-malignant Pancreatic Disease	2.07 (1.56, 2.75)
Skin Infections/Abscesses	1.14 (1, 1.3)
Sleep Apnea	1.33 (1.16, 1.52)
Bipolar Disorder/Schizophrenia	2.85 (2.44, 3.32)
Chronic Headache	1.73 (1.57, 1.9)

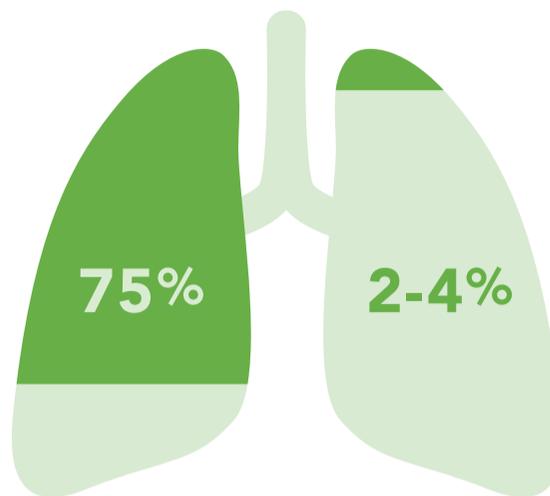
medical users of prescription opioids who were at increased risk of an opioid-induced respiratory depression or overdose event.⁴⁰

Comorbidities

Based on the aforementioned studies, it is clear that patients taking opioids with certain comorbidities are at increased risk for life-threatening OIRD and overdose. These include those with chronic respiratory diseases (e.g., sleep apnea, severe asthma and COPD), cardiovascular disease, psychiatric disorders (e.g., bipolar, schizophrenia) and prior substance use disorder.⁴¹⁻⁴³

The relationship of these comorbidities and propensity towards experiencing life-threatening OIRD in users of prescription opioids is understandable for certain comorbidities. For example, there is a high prevalence of sleep-disordered breathing in opioid-treated chronic pain patients. Obstructive and central sleep apnea syndromes occurred in 75% of one study population, compared to 2%-4% of the general population.⁴⁴ A distinct region within the medulla has been identified that is associated with opioid-induced suppression of tongue muscle activity and opioids have been demonstrated to have an inhibitory effect on the hypoglossal motor neuron, which can result in potentially fatal upper airway obstruction.²⁷ Additionally, the effects of opioids on the airway and respiratory muscles are compounded in individuals with sleep apnea, who have a predisposition to hypoxemia or hypercapnia during sleep.

Hepatorenal impairment has also been shown to increase life-threatening OIRD. Increased peak levels and plasma concentrations of morphine, oxycodone and their respective active metabolites have been reported in patients with liver



Obstructive and central sleep apnea syndromes occurred in 75% of one study population of opioid-treated chronic pain patients, compared to 2%-4% of the general population.

disease. This has been associated with an increased risk of adverse events. The accumulation of glucuronide metabolites due to dramatically reduced renal clearance of morphine, oxycodone and codeine metabolites in patients with renal disease has been reported to cause respiratory depression, and should be avoided in patients requiring dialysis. However, some opioids, such as fentanyl and methadone, have been reported to be minimally affected by kidney or liver disease.²⁷

Individuals with a history of any substance use disorder, who are dispensed opioids, are nearly thirteen times more likely to experience an opioid emergency within the next six months.²⁰ Chronic pain patients frequently report greater depression and anxiety as compared with patients with other medical conditions. Greater pain intensity and poorer function are also reported among chronic pain patients with a severe mood disorder, and patients at higher risk for opioid abuse also tend to have higher rates of mood disorders. Some of the

TABLE 2: Risk Assessment for Overdose or Serious Opioid-Induced Respiratory Depression

Step 1: Determine Score for Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD)

Question ¹	Points for "Yes" Response
In the past 6 months, has the patient had a healthcare visit (outpatient, inpatient or ED) involving ANY OF THE FOLLOWING HEALTH CONDITIONS?²	
Substance use disorder (abuse or dependence)? <i>*includes opioids, antidepressants, sedatives/ anxiolytics, alcohol, amphetamines, cannabis, cocaine, hallucinogens</i>	25
Bipolar disorder or schizophrenia?	10
Stroke (cerebrovascular accident, CVA) or other cerebrovascular disease?	9
Chronic kidney disease with clinically significant renal impairment?	8
Heart failure?	7
Non-malignant pancreatic disease (e.g., acute or chronic pancreatitis)?	7
Chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis)?	5
Chronic headache (e.g., migraine)?	5
DOES THE PATIENT CONSUME:	
Fentanyl? (e.g., transdermal or transmucosal immediate-release products)	13
Morphine?	11
Methadone?	10
Hydromorphone?	7
An extended-release or long-acting (ER/LA) formulation of any prescription opioid, including the above? ³	5
A prescription benzodiazepine? (e.g., diazepam, alprazolam)	9
A prescription antidepressant? (e.g., fluoxetine, citalopram, venlafaxine, amitriptyline)	8
Is the patient's current maximum prescribed opioid dose \geq 100 mg morphine equivalents per day? (Include all prescription opioids consumed on a daily basis)	7
Total point score (maximum 146)	

Step 2: Identify Risk Class for OSORD

Risk Class	RIOSORD Score (Points)	Average Probability of OSORD
1	0-4	2%
2	5-7	5%
3	8-9	7%
4	10-17	15%
5	18-25	30%
6	26-41	55%
7	\geq 42	83%

OSORD, overdose or serious opioid-induced respiratory depression

¹ This questionnaire is intended for completion and interpretation by a healthcare professional. It is not a replacement for clinical judgment and is intended to guide and inform clinical decision-making for patients who are prescribed opioids.

² The condition does not have to be the primary reason for the visit but should be entered in the chart or EHR as one of the reasons or diagnoses for the visit.

³ A patient consuming 1 or more opioids with an ER/LA formulation receives 5 additional points for 'ER/LA formulation of any prescription opioid' regardless of the number of different ER/LA products consumed.

use of opioids in patients with mood disorders is thought to be for treatment of the mood disorder and not necessarily as a substance abuse disorder as the substance abuse problem abates once the mood disorder is properly treated.⁴⁵

Concomitant Medications

When opioids are combined with certain concomitant medications such as CNS depressants (e.g., benzodiazepines), sedatives such as antihistamines or muscle relaxants and medications affecting cytochrome P450 (CYP-450) metabolism which includes macrolide antibiotics (e.g., erythromycin) and MAO-inhibitors, the risk for life-threatening OIRD or overdose is also significantly increased.⁴⁶⁻⁴⁸ The Substance Abuse and Mental Health Services Administration's (SAMHSA) Center for Behavioral Health Statistics and Quality Drug Abuse Warning Network (DAWN) has stated that the risk of hospitalization or death is substantially higher in patients taking benzodiazepines with opioids which is consistent with the Zedler studies.^{20,40}

Many of these concomitant medications are prescribed by multiple physicians. This is important as studies examining opioid-related fatalities demonstrate two-thirds of patients taking a dangerous combination of an opioid with another prescription are prescribed medications by two or more HCPs.⁴⁹ In addition, there is evidence that drug-drug interactions involving the CYP450 system and p-glycoprotein are more common than previously appreciated.^{50,51}

Social and Behavioral Factors

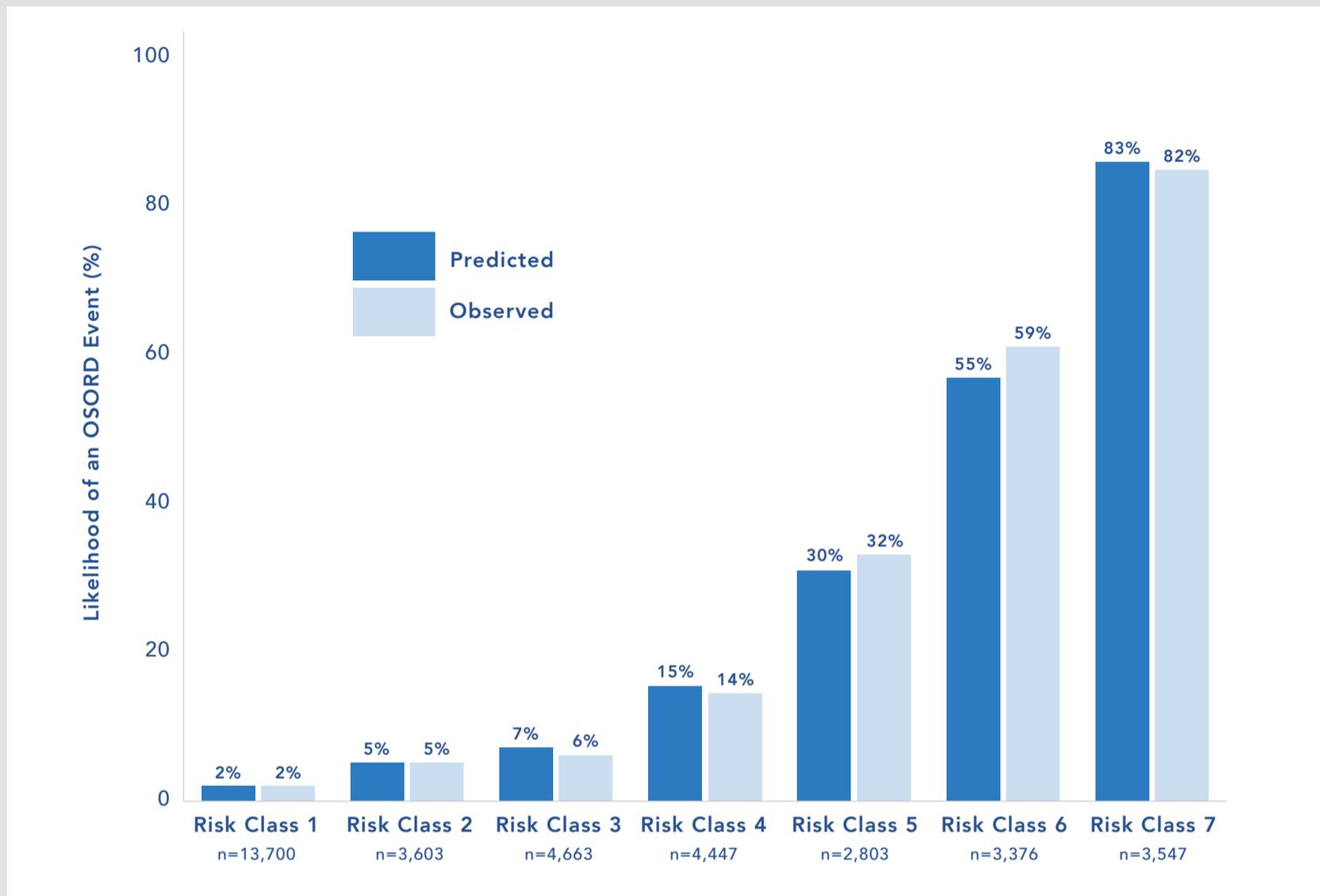
Patient specific behavioral factors can also contribute to having increased risk. These include age, gender, obesity, ethnicity, genetics, social history

and alcohol use.^{25,52} Consuming alcohol with opioids has an additive depressant effect and may result in unintentional opioid accelerated release, also known as dose dumping.^{53,54} Unintentional exposure and ingestion of opioids by family members can also occur. On average, 3,300 children ≤ 5 years old are admitted to the emergency room each year due to accidental opioid exposure.⁵⁵ In 2011 alone, 5,187 children ≤ 5 years of age were admitted to emergency departments.⁵⁶

Opioid-specific Factors

Specific opioid-related factors also place patients at increased risk of life-threatening OIRD and overdose. These include taking high opioid dosages, initiation of opioid treatment, titration of opioid dosage for continued pain control, rotation from one opioid to another and using more than one opioid concomitantly.^{41,42} Two separate studies looked at risk as a function of average daily opioid dose received at the time of overdose. All opioid doses were converted into morphine-equivalent doses using equianalgesic conversions and plotted against a hazard ratio as a measurement of risk. Both studies showed an increase in risk rises dramatically between doses of 50 and 100 mg/day and a further increase with doses above 100 mg/day.^{41,47} This is consistent with the Zedler study which demonstrated that those with a maximum prescribed daily MED greater than or equal to 100 mg/day were more than twice as likely to experience a serious opioid-induced respiratory depression or overdose event compared to matched controls. Certain preparations of opioids have also been demonstrated to increase one's risk including extended-release and long-acting (ER/LA) opioids, morphine, methadone and fentanyl, as well as

TABLE 3: Predicted Probability (Risk Classes, by Percentiles) vs Observed Incidence of Overdose or Serious Opioid-induced Respiratory Depression



specific techniques of opioid administration such as intrathecal opioid pain pumps.^{20,42,57,58}

Prescribing information for ER/LA opioids contain a **BOXED WARNING** alerting prescribers and patients to serious or even fatal effects that can occur. These warnings include:^{59,60}

- The opioid exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death
- Serious, life-threatening or fatal respiratory depression may occur with use
- Accidental ingestion of even one dose, especially by children, can result in a fatal overdose
- Concomitant use with all cytochrome P450 inhibitors may result in an increase in opioid plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression
- Consuming with alcohol may result in increased plasma levels and a potentially fatal overdose

Warnings and precautions for other opioids also contain similar language.⁶¹

FIGURE 4



5 Early Intervention Is Critical During An Opioid Emergency

+ Opioid Toxidrome Triad – includes altered mental state, OIRD and miosis.

+ Average time for EMS response in America is 9.4 minutes.

+ Most life-threatening opioid emergencies occur in the home and are witnessed by friends and family who may be in the best position to intervene quickly.

+ When life-threatening OIRD occurs, oxygen levels in the blood system decrease and can negatively affect the CNS, including the potential for brain damage to occur in as little as 3-4 minutes.

+ Seconds count during an opioid emergency. Those most likely to witness an opioid emergency should be provided education of signs and symptoms as well as the importance of an opioid emergency action plan.

The clinical signs of a life-threatening OIRD or overdose event are known as the Opioid Toxidrome Triad. The Toxidrome are the signs and symptoms most commonly seen with an opioid overdose. The Toxidrome consists of (i) altered mental state—drowsiness or coma, (ii) OIRD—decreased tidal volume and/or decreased respiratory rate, and (iii) miosis—pinpoint pupils.⁶² Additional signs of an opioid-related overdose can include (i) pale and clammy face, (ii) limp body, (iii) fingernails or lips turning blue/purple, (iv) vomiting or gurgling noises, (v) cannot be awakened from sleep or is unable to speak, and (vi) heartbeat is very slow or stopped.⁶³ The point can be made that you don't need to be a highly trained professional to recognize the signs of OIRD and overdose.

When life-threatening OIRD occurs, oxygen levels in the blood system decrease enough to negatively affect the CNS. Structures of the CNS particularly vulnerable to hypoxia are structures

associated with coordination and movement, Purkinje fibers of the cerebellum and the Parieto-occipital cortex, and structures associated with memory, the Hippocampus.⁶⁴ Post-anoxia morbidity and recovery are dependent of the extent of injury. Possible post-anoxia events/symptoms can be associated with (i) short-term memory loss, (ii) poorer performance in executive functions, (iii) anomia, (iv) visual disturbances, ataxia or movement disorders, (v) confusion, depression or personality changes, and (vi) seizures.^{65,66}

After severe anoxia of at least 4 minutes' duration, arrhythmias and asystole often develop, causing decreased cardiac output and decreased brain perfusion, compounding the already decreased oxygen levels in the brain.⁶⁷ When there is a lack of blood flow to the brain for more than 3-4 minutes, brain damage will be fairly generalized throughout both the cerebral and cerebellar cortex and will also involve subcortical structures

Most life-threatening opioid emergencies occur in the home and are witnessed by friends and family who may be in the best position to intervene quickly.

such as the basal ganglia.⁶⁸ The average emergency medical services time to arrive on scene of an emergency following dispatch for adults has been estimated at 9.4 minutes.⁶⁹ When seconds count in resuscitating an individual, this disparity can be insurmountable.

Most life-threatening opioid emergencies occur in the home and are witnessed by friends and family who may be in the best position to intervene quickly.²⁹ Given this, it makes intuitive sense to reduce the time it takes to get emergency treatment to a patient by equipping those best positioned to respond rapidly with the proper knowledge on how to recognize and treat an opioid emergency.⁷⁰

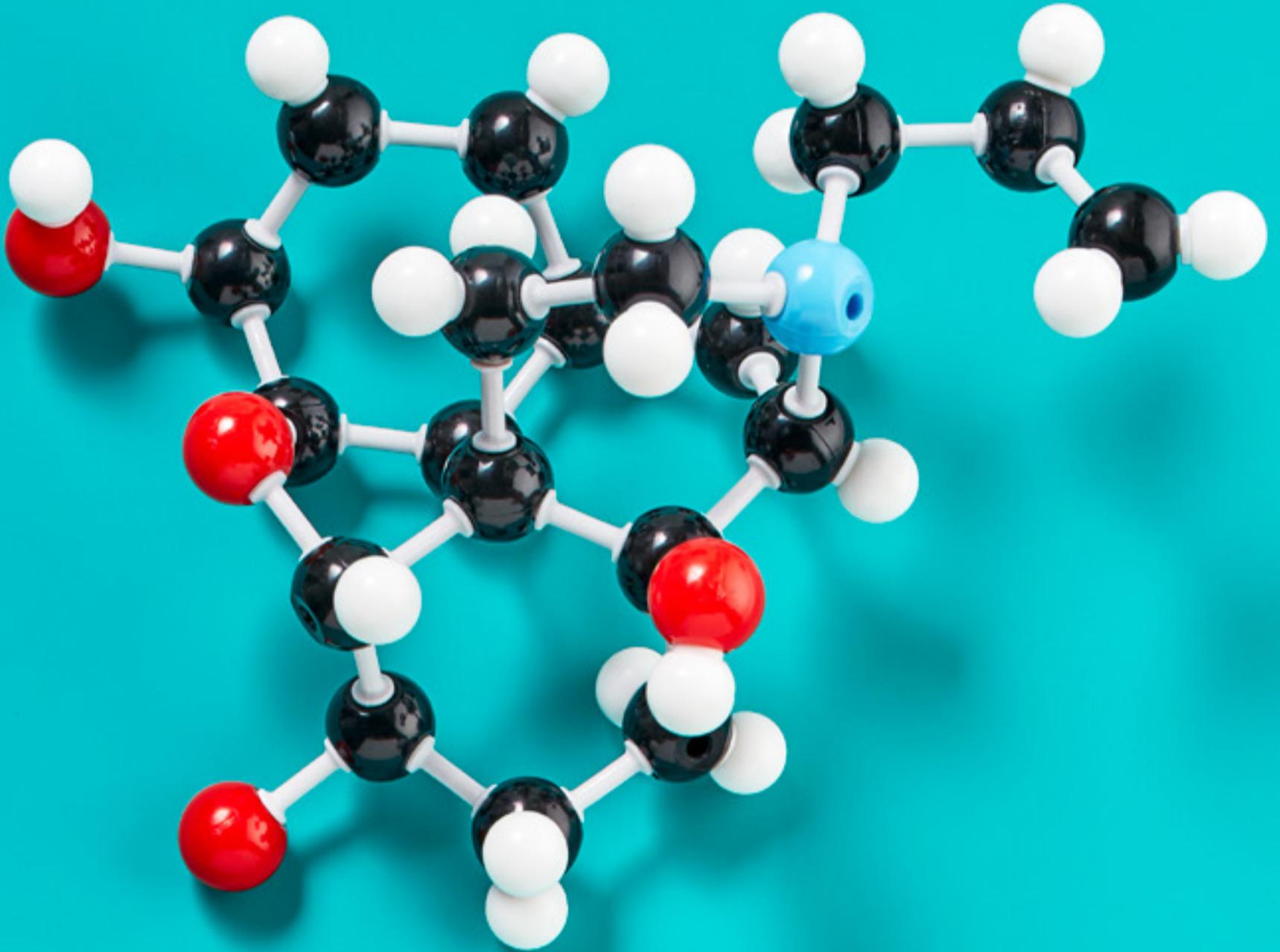
Strategies to Reduce Opioid-related Morbidity and Mortality

Several strategies are used by the pharmaceutical industry as well as certain government agencies to help curb the abuse and misuse of prescription opioids as well as the use of heroin. These strategies

include healthcare provider education and training, stricter labeling and adoption of risk evaluation and mitigation strategies (REMS) for certain classes of opioids, the development of abuse-deterrent opioid formulations, use of prescription drug monitoring programs (PDMPs) and urine drug testing as a part of opioid prescribing practices as well as encouraging the use of pain management agreements. However, these measures have been limited in their ability to reduce opioid-related morbidity and mortality as demonstrated by the continued rise in opioid-related deaths and do not address the risk of an opioid emergency in patients who are using opioids medically for a diagnosed pain condition.⁷¹ Additionally, it is this group of patients who are taking opioids chronically for pain, who have never been diagnosed with an underlying opioid use disorder, that represent the largest number of opioid users, has the highest magnitude of opioid-related harm and are the least well-served by current anti-harm initiatives with respect to opioid emergency preparedness.^{39,71}



::: FIGURE 5



Naloxone

($C^{16}H^{21}NO^4$)

6 Naloxone – Standard of Care for Life-threatening OIRD

+ Naloxone HCl injection was first approved in 1971, initial labeling as IV/SC/IM dosing from 0.4 mg – 2mg given every 2-3 minutes.⁷²

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

+ The duration of action is dependent upon the dose and route of administration of naloxone, but is less than the effects of prescribed opioids.

+ Naloxone has a higher affinity for mu receptors than traditional opioids, enabling naloxone to displace opioid molecules at the receptor sites and to prevent binding of opioids.⁷³

History of Naloxone Hydrochloride

Naloxone HCl injection was originally approved in 1971. Over the last four decades, naloxone has been primarily utilized in emergency room or healthcare settings. As the opioid epidemic began around a decade ago, individuals in the harm reduction community began educating harm reduction/needle exchange clinics on overdose awareness and treatment. These education programs, which included education of naloxone administration, have reduced the potential of opioid-related death rates.^{71,74} However, naloxone's potential to reduce fatalities from life-threatening OIRD and overdose have been constrained by a lack of education within

the healthcare provider community, the limited number of pilot distribution programs among the harm reduction and law enforcement communities, as well as passive distribution programs in the pharmacy setting.⁷³ Most programs have focused on the illicit opioid abuse population and are not widely available for patients with opioid prescriptions being used for medical reasons.^{73,75} Furthermore, many naloxone distribution programs are located at needle exchange programs, making it unlikely for non-injection drug users, legitimate patients or individuals without access to these programs to participate.

There are now three categories of naloxone available, naloxone formulations developed and



intended for trained healthcare professionals (e.g. Emergency Medical Technicians, Nurses, Physicians), “take-home” naloxone products that were developed, designed, approved and labeled for use in non-medical settings such as the home by laypersons (i.e. family members and caregivers), and other naloxone products.

Naloxone for Medical Settings

a. Indication

For the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic narcotics, propoxyphene, methadone and certain narcotic-antagonist analgesics: nalbuphine, pentazocine and butorphanol. Naloxone hydrochloride injection is also indicated for the diagnosis of suspected acute opioid overdosage and as an adjunctive agent to increase blood pressure in the management of septic shock.

b. Dosage Forms

- Single-dose and multi-dose vials
- Single dose glass ampoules
- Single-dose prefilled glass cartridges for injection

c. Other information

These products require a needle and syringe for manual administration and/or assembly with a separate needle attachment for IM or SC administration. In addition, they do not include patient information leaflets or trainers to help patients train caregivers for use outside a medical setting.

Take-Home Naloxone

a. Indication

These products are indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. They are also intended for immediate administration as emergency therapy in settings where opioids may be present and are not a substitute for emergency medical care.

b. Dosage Forms

- Single-dose prefilled auto-injector of 0.4 mg naloxone HCl injection (FDA Approved April 3, 2014)⁷⁶
- Single-dose prefilled nasal spray of 4 mg naloxone HCl (FDA Approved November 19, 2015)⁷⁷

c. Other information

These products are distinct from the naloxone formulations used in medical settings as they were specifically designed for layperson use using a development program incorporating human factors engineering principles and associated usability assessments. Both are pre-assembled, ready-to-use products that include information leaflets for patients and laypersons. The naloxone auto-injector also includes a Trainer for practice to help train others on proper administration prior to an opioid overdose emergency.

Other Naloxone Products

Pre-hospital emergency personnel, harm reduction programs and a small number of pharmacies have, in addition to providing syringe/needle based kits, adapted the injectable glass cartridge form of naloxone for intranasal administration via the attachment and assembly of a mucosal atomizer in order to increase accessibility to naloxone in the community setting.⁷³ The intranasal route of delivery, when using injectable naloxone modified with a nasal atomizer is not an FDA approved combination product, has very limited data on safety or efficacy,⁷⁵ and requires multiple steps for assembly.

In general, while the intranasal route of administration has shown promise among case reports of life saves in the community; questions remain regarding its efficacy in certain populations. Administering naloxone with the nasal mucosa via syringe + nasal atomizer has reported contraindications in the literature, including being contraindicated in patients with: (i) excessive nasal mucous, (ii) nasal septum abnormalities, (iii) nasal trauma, (iv) epistaxis, (v) intranasal damage caused by the use of substances such as cocaine,

Naloxone is not a substitute for emergency medical care.

(vi) severe hypertension, and (vii) recent use of vasoconstrictors.^{78,79}

Use of the nasal atomizer to deliver naloxone has less than a 75% success rate for reversing respiratory depression in two frequently cited published studies.^{80,81}

Pharmacology

Naloxone hydrochloride [$C_{16}H_{21}NO_4HCl$; M.W. 363.84] 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. Naloxone is used for the treatment of an opioid emergency, such as an overdose or a potential opioid overdose, with signs of respiratory or central nervous system depression. Naloxone is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites. Naloxone has a higher affinity for mu receptors than traditional opioids, enabling naloxone to displace opioid molecules at the receptor sites and to prevent binding of opioids.⁷³

This reverses the effects of opioids, including respiratory and central nervous system depression and hypotension. Naloxone can also reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine. Naloxone only works when a person has opioids in their system and has no clinical effect if opioids are absent. Naloxone has not been shown to produce tolerance nor to cause physical or psychological dependence and is a non-scheduled prescription medication, meaning it is considered to have no potential for abuse by the U.S. Drug Enforcement Administration (DEA). The duration of action is dependent upon the dose and route of administration of naloxone, but is less than the effects of prescribed opioids.



Bystanders can and will use naloxone to reverse opioid overdose when properly trained.

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine 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.

A Review of the Safety and Efficacy of Naloxone for the Treatment of OIRD

Efficacy of Naloxone

Naloxone has been shown to be effective when used by healthcare professionals. There are no trials specifically evaluating the effectiveness of naloxone when administered by nonmedical first responders such as police officers and firefighters. A recent prospective study of naloxone use by law enforcement demonstrated a potential correlation in decreased mortality from opioids with naloxone provision and administration by police first responders. Although there is ample evidence supporting the

safety and efficacy of naloxone for the treatment of opioid overdose, less is known about the effectiveness of naloxone used by individuals other than trained first responders and healthcare professionals.

There have been a number of non-randomized studies evaluating the effectiveness of community-based overdose prevention programs that include the distribution of naloxone to nonmedical personnel. For example, from 1996 through June 2014, a total of 644 local sites in 30 states and the District of Columbia reported providing naloxone kits to 152,283 laypersons and receiving reports of 26,463 drug overdose reversals using naloxone from 1996 through June 2014. Most laypersons who reported using the kits to reverse an overdose were persons who use drugs, and many of the reported reversals involved heroin overdoses.⁸² In a comprehensive review, Clark and colleagues concluded that bystanders (mostly opioid users) can and will use naloxone to reverse opioid overdose when properly trained, and that this training can be done successfully through these programs. The authors acknowledge that the lack of randomized controlled

Reversal of respiratory depression by partial agonists such as buprenorphine may be incomplete and may require large doses of naloxone.

trials of community-based overdose prevention programs limits conclusions about their overall effectiveness.⁸³

Safety of Naloxone

When given to individuals who are not opioid-intoxicated or opioid-dependent, naloxone produces no clinical effects, even at high doses. Moreover, while rapid opioid withdrawal in tolerant patients may be unpleasant, it is not life-threatening. Naloxone can safely be used to manage opioid overdose in pregnant women. The lowest dose to maintain spontaneous respiratory drive should be used to avoid triggering acute opioid withdrawal, which may cause fetal distress.

Precipitation of Severe Opioid Withdrawal

The use of naloxone 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.

In the post-operative setting, 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.

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.

7 Expanding Access to Naloxone: Select Organizational Support

Many organizations strongly recommend that naloxone be readily accessible to individuals likely to witness a life-threatening opioid emergency. These include world, federal, state and medical professional organizations. Below are selected statements from leading organizations relating to the call for expanded naloxone access, including co-prescription with opioids for patients deemed to be at increased risk for life-threatening OIRD or overdose.

World Health Organization – Community Management of Opioid Overdose⁸⁴

Introduction

In 2012, the United Nations Economic and Social Council (ECOSOC) called upon the World Health Organization (WHO), in collaboration with the United Nations Office on Drugs and Crime (UNODC) to provide advice and guidance, based on scientific evidence, on preventing mortality from drug overdose, in particular opioid overdose [WHO 2014]. These guidelines aim to reduce the number of deaths from opioid overdose by providing evidence-based recommendations on the availability of naloxone for people likely to witness an opioid overdose along with advice on the resuscitation and post-resuscitation care of opioid overdose in the community.

Specifically, these guidelines seek to:

- Increase the availability of naloxone to people

likely to witness an opioid overdose in the pre-hospital setting

- Increase the preparedness of people likely to witness an opioid overdose to respond safely and effectively by carrying naloxone and being trained in the management of opioid overdose
- Increase the rate of effective resuscitation and post-resuscitation care by persons witnessing an opioid overdose

Summary of Recommendations

People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose.

- Naloxone is effective when delivered by intravenous, intramuscular, subcutaneous and intranasal routes of administration. Persons using naloxone should select a route of administration based on the formulation

available, their skills in administration, the setting and local context.

- In suspected opioid overdose, first responders should focus on airway management, assisting ventilation and administering naloxone.
- After successful resuscitation following the administration of naloxone, the level of consciousness and breathing of the affected person should be closely observed until full recovery has been achieved.

Most opioid overdoses occur in private homes, and most of these are witnessed. Close friends, a partner or family members are most likely to witness an opioid overdose. Death in opioid-overdose can be averted by emergency basic life support resuscitation and/or the timely administration of an opioid antagonist such as naloxone.

State Medical Board Example: Medical Board of California⁸⁵

http://www.mbc.ca.gov/licensees/prescribing/pain_guidelines.pdf

- Empirical evidence has shown that lay persons can be trained to recognize the signs of an opiate overdose and to safely administer naloxone, an opiate antagonist.
- Effective January 1, 2015, California pharmacists are able to furnish an opioid overdose reversal drug in accordance with standardized procedures or protocols, naloxone, to family members of patients at risk for overdose, those who might be in contact with an individual at risk

Lay persons can be trained to recognize the signs of an opiate overdose and to safely administer naloxone.

for overdose, or anyone who requests the drug without a prescription.

- Appendix 12 – Suggested Language on Naloxone for Pain Management Agreement
 - » I understand that “overdose” is a risk of opioid therapy which can lead to death. I understand and can recognize the signs and symptoms of overdose including respiratory depression.
 - » I understand that I will be prescribed naloxone because overdose is a risk of opioid therapy. I understand that naloxone is a drug that can reverse opioid overdose. I understand when and how to use naloxone.
 - » I understand it is strongly encouraged to share information about naloxone with my family and friends.
 - » I understand it is strongly encouraged to teach family and friends how to respond to an overdose.

Substance Abuse and Mental Health Services Administration (SAMHSA) – Opioid Overdose Toolkit⁶⁰

Introduction

SAMHSA, a division of HHS had developed an Opioid Overdose Toolkit to serve as a resource for patients, family members, first responders as well as healthcare providers. In 2014, SAMHSA updated their Opioid Overdose Toolkit and revised their criteria relating to at-risk patients.

Highlights from SAMHSA Opioid Overdose Toolkit

Strategies to prevent overdose deaths

Strategy 1:

Encourage providers, persons at high risk, family members and others to learn how to prevent and manage opioid overdose.

Strategy 2:

Ensure access to treatment for individuals who are misusing or addicted to opioids or who have other substance use disorders.

Strategy 3:

Ensure ready access to naloxone.

Strategy 4:

Encourage the public to call 911.

Strategy 5:

Encourage prescribers to use state Prescription Drug Monitoring Programs (PDMPs).

Consider Prescribing Naloxone along with the Patient's Initial Opioid Prescription

Naloxone competitively binds opioid receptors and is the antidote to acute opioid toxicity. With proper

education, patients on long-term opioid therapy and others at risk for overdose may benefit from having [naloxone] that can be carried in a pocket or stored in a medicine cabinet to use in the event of known or suspected overdose.

Those at risk for overdose may benefit from having naloxone that can be carried in a pocket or stored in a medicine cabinet to use in the event of known or suspected overdose.

Patients who are candidates for such kits include those who are:

- Taking high doses of opioids for long-term management of chronic malignant or non-malignant pain.
- Receiving rotating opioid medication regimens (and thus are at risk for incomplete cross-tolerance).
- Discharged from emergency medical care following opioid intoxication or poisoning.
- At high risk for overdose because of a legitimate medical need for analgesia, coupled with a suspected or confirmed history of substance abuse,

dependence, or non-medical use of prescription or illicit opioids.

- On certain opioid preparations that may increase risk for opioid overdose such as extended release/long-acting preparations.
- Completing mandatory opioid detoxification or abstinence programs.

Legal and Liability Considerations

Health care professionals who are concerned about legal risks associated with prescribing naloxone may be reassured by the fact that prescribing naloxone to manage opioid overdose is consistent with the drug’s FDA-approved indication, resulting in no increased liability so long as the prescriber adheres to general rules of professional conduct.

American Medical Association (AMA)^{86,87}

Introduction

The American Medical Association has become increasingly focused on the Opioid Overdose Epidemic, including the role of naloxone in potentially reducing Opioid-related morbidity and mortality. They have testified on capitol hill regarding the potential for naloxone to save additional lives, have presented in front of the FDA regarding approaches to combat the opioid overdose epidemic, and have formed an Opioid Abuse Task Force which is advocating for the co-prescription of naloxone to patients at increased risk.

Representative AMA Support

“The AMA and many community, state and national groups—including professional organizations, government bodies and industry organizations—have supported co-prescribing naloxone to patients who are taking opioids as a critical part of the solution to the rising epidemic of opioid-overdose related deaths.

The AMA encourages physicians to co-prescribe naloxone to their patients at-risk who are taking opioid analgesics.

Increased access to naloxone is a key element of a comprehensive public health approach to decrease prescription drug overdose. The AMA believes that co-prescription of naloxone and enhanced access to this medication in community-based programs—coupled with increased use of prescription drug monitoring programs and enhanced education and awareness about the number of opioid emergencies—are critical next steps in reversing the growing epidemic of opioid-related morbidity and mortality.”

– Patrice A. Harris, MD,
chair-elect of the AMA Board of Trustees

The AMA encourages physicians to co-prescribe naloxone to their patients at-risk who are taking opioid analgesics.



“The Task Force encourages physicians to consider prescribing naloxone when it is clinically appropriate to do so. Several factors that may be helpful in determining whether to co-prescribe naloxone to a patient, or to a family member or close friend of the patient, include:

- Is my patient on a high opioid dose?
- Is my patient also on a concomitant benzodiazepine prescription?
- Does my patient have a history of substance use disorder?
- Does my patient have an underlying mental health condition that might make him or her more susceptible to overdose?
- Does my patient have a medical condition, such as a respiratory disease or other co-morbidities, that might make him or her susceptible to opioid toxicity, respiratory distress or overdose?
- Might my patient be in a position to aid someone who is at risk of opioid overdose?

Opioid overdose is most often accidental and can occur in patients with and without substance use disorders. Naloxone can save lives. Co-prescribing requires that physicians are prepared to educate their patients (and families/loved ones) on the risk and what to do in case of overdose. The Task Force also acknowledges that a decision to co-prescribe naloxone may raise difficult issues for some physicians, including how to have a discussion about the risk of overdose; the potential stigma a patient may feel; how to engage the patient in broader discussions about treatment for a substance use disorder, if applicable; and how to ensure the patient (or close friend/family member) has the appropriate training to act in case of an overdose.”

Opioid overdose is most often accidental and can occur in patients with and without substance use disorders. Naloxone can save lives.



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