Naloxone Meeting

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

5 October 2016

Kaleo Pharmaceuticals
Richmond, VA

kaléo

Naloxone HCl Products for Use in the Community Setting

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Presentation Overview

- **Introduction to kaléo**
- **The Opioid Epidemic in the United States**
- **Use of Naloxone in the Community**
- **Important Characteristics for Naloxone HCl Products Used in the Community**
- **Advisory Committee Points for Discussion Summary**

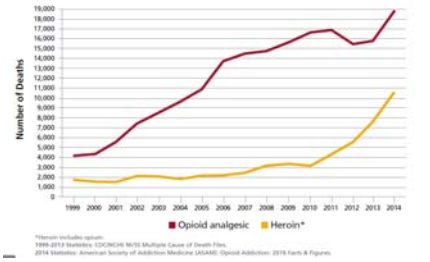
Introduction to kaléo

To provide innovative medical products that help empower patients and caregivers to confidently take control in potentially life-threatening situations

- **Privately-held pharmaceutical company**
- **Kaléo products combine an established drug, an innovative delivery platform and exceptional quality**
- **2 FDA Approved Products**

The Opioid Epidemic in the United States

U.S. Deaths from Opioids & Heroin: 1999-2014



Opioid-related toxicity occurs across sex, ethnic, age and geographic strata, and includes both medical and non-medical opioid use

"THIS IS UNPRECEDENTED': 174 HEROIN OVERDOSES IN 6 DAYS IN CINCINNATI" (AUGUST 2016) WASHINGTON POST

"The culprit responsible for the staggering number was probably heroin cut with the latest opioid boost meant to deliver consumers a stronger, extended high — carfentanil."

http://www.kgw.com/news/fentanyls-deadlier-cousin-a-few-grains-of-carfentanyl-can-kill/296315308

Kaléo's Position on Points of Discussion

- **The benefit of administering naloxone in the community setting at any dose far outweighs the risk**
- **Opioid dependent neonates are best treated in healthcare facilities with access to titratable naloxone formulations**
- **One dose per route will avoid confusion for clinicians and patients**
- **Potential for serious risk to patients:**
  - Hesitation in prescribing or administering due to dosing confusion
  - Products that cannot be quickly and easily used
  - Real world situations that impact pharmacokinetics (e.g., common nasal medications, nasal abnormalities)

Use of Naloxone HCl in the Community Setting

Product	EVZIO® (naloxone HCl injection, USP) Auto-injector	NARCAN® (naloxone HCl) Nasal Spray	IN Naloxone Kit (not FDA Approved)
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
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 4.0 mg per dose IN	2 mg/2 mL IN; dose 1 mL/ nostril 2 mg per dose IN
Features	• Written instructions • No assembly required • Auto-retractable needle • Trainer for practice included • Voice and visual instruction system, including audible reminder to seek emergency medical attention	• Written instructions • No assembly required • Needleless intranasal delivery • No Trainer for practice included	• Written instructions • Assembly required • Needleless intranasal delivery • No Trainer for practice included

EVZIO – naloxone HCl injection, solution. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=df501ed0-c0f4-11e3-8a33-0800200c9a66
NARCAN – naloxone HCl spray. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=724df050-5332-4d0a-9a5f-17bf08a547e1
http://harmreduction.org/issues/overdose-prevention/overview/overdose-basics/understanding-naloxone/

Treatment Algorithm (Community Setting)

- **Caregiver/layperson Initial Treatment**
  - Administer initial dose of naloxone HCl
  - Seek emergency medical attention
  - Administer repeat doses every 2-3 minutes as needed to keep patient breathing until emergency medical services (EMS) arrives
- **EMS/Transport**
  - Administer additional naloxone as needed
  - Provide additional supportive and resuscitative care
- **Hospital Care**
  - Definitive medical care in emergency room/ hospital setting until complete resolution of opioid emergency
  - Follow-up care as required depending on nature of incident

(NEDARC. Average Adult EMS Times (19-100+ years of age) National EMS Information System (NEMSIS Data).2010.

Safety of Naloxone HCl for Dose Considerations

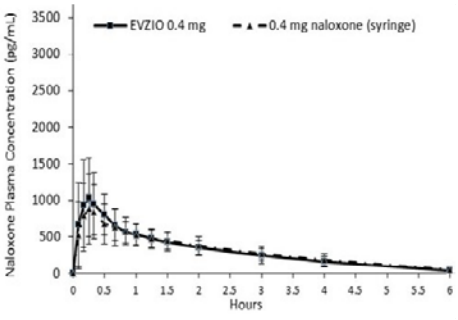
- **High safety margin for naloxone**
  - No upper limit for incremental doses
  - Safety demonstrated at maximum concentrations 5 to 25 fold higher than products currently used in the community setting
- **No pharmacological effect in the absence of opioids**
- **Precipitation of acute withdrawal symptoms is preferable to the potentially life-threatening consequences of hypoxia**
- **Cardiovascular and Pulmonary Adverse Events**
  - Observed in patients with pre-existing cardiac disease or in post-operative settings
  - No direct cause and effect has been linked to naloxone

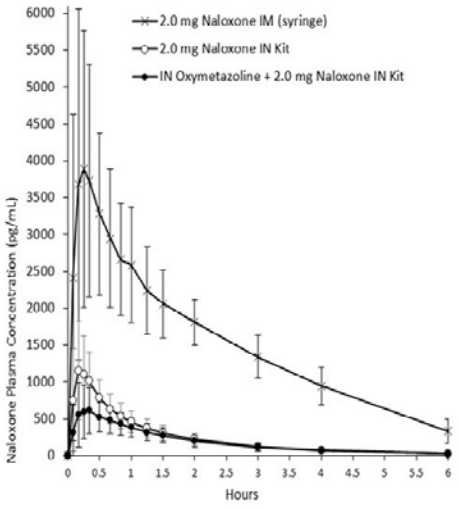
Pharmacokinetics of Naloxone HCl

- **Absorption and Distribution**
  - Rapidly absorbed from injection sites
  - Exhibits rapid transport into and out of the brain
  - Subject to first pass metabolism (oral)
  - Weakly bound to plasma proteins
  - Found in the brain, kidney, spleen, lung, heart, and skeletal muscle
- **Metabolism and Excretion**
  - Almost completely metabolized
  - Glucuronide conjugation is the main route of metabolism in man
  - Excreted in the urine or in bile
- **Half Life**
  - Adults: ~1.3 – 2.1 hours
  - Neonates: 3.1 hours
- **Bioavailability**
  - **IM/SC**: ~36% compared to IV
  - **IN**: ~ 5% – 17% compared to IV (14.6% – 46.7% compared to IM)
  - **Oral**: ~ 2% compared to IV

Pharmacokinetics of Naloxone HCl

- **EVZIO 0.4 mg has comparative bioavailability to reference product**
- **Significantly lower relative bioavailability of IN compared to IM**
- **Common over-the-counter nasal vasoconstrictor significantly impacts intranasal naloxone exposure**





Naloxone Exposure Across Administration Routes

- **Safety demonstrated with naloxone exposure at higher levels than products used in the community setting**
- **Current minimum FDA approved threshold – 0.4 mg syringe**
- **Vasoconstrictor can significantly impact intranasal bioavailability**

Route	Dose	C_{max} (pg/mL)	T_{max} (hr)	AUC_{last} (hr-pg/mL)	$T_{1/2}$ (hr)	Ref
IV	0.035 mg/kg	25,270 ± 11,660*	0.05	12,730 ± 2,550*	NR	1
IN	20 mg crushed powder	20,150 ± 5,710*	0.28	29,930 ± 12,470*	NR	1
IN	4 mg (NARCAN®)	4,830 (43.1%)	0.5	7,950 (37.3%)	2.08 (29.5%)	2
IM	2 mg (syringe)	4,150 (43.9%)	0.25	9,669 (13.6%)	1.47 (24.2%)	3
IN	2 mg (offlabel kit)	1,163 (47.5%)	0.25	1,411 (35.7%	1.44 (17.2%)	3
IM/SC	0.4 mg (EVZIO®)	1,100 (52.4%)	0.25	1,680 (24.7%)	1.22 (29.2%)	4
IM/SC	0.4 mg (syringe)	857 (53.2%)	0.33	1,810 (27.8%)	1.32 (22%)	4
IN	2 mg + oxy (offlabel kit)	571 (48.9%)	0.33	1,077 (35.3%)	1.46 (20.7%)	3

* = data presented as mean ± SD. Other data presented as geometric mean (gCV%)

1-TARGINIQ® ER – Summary Basis of Approval, NDA 205777, Clinical Pharmacology and Biopharmaceutics Review, 2014
2-NARCAN Nasal Spray – Summary Basis of Approval, NDA 208411, Clinical Pharmacology and Biopharmaceutics Review, 2015
3-Kaleo, Inc. Clinical Study Report IJ-901DV-03O
4-Kaleo, Inc. Clinical Study Report IJ-900DV-03O

Important Characteristics for Naloxone Products Used in the Community

Products for Use in Community	EVZIO
• Quickly and easily usable by non-medical individuals (e.g., intuitive)	• Voice and visual prompts to aid user through injection process • Trainer included in each carton
• Easily carried/portable	• Pocket-sized, single use, auto-injection system
• Ruggedly designed	• Tested to ensure delivery of accurate dose under “real world” conditions
• Provide a safe and efficacious dose	• Two auto-injectors included in each carton • Auto-retractable needle
• Product and labeling to prompt user to seek medical attention	• Voice prompt instruction to “seek medical attention” post-injection

Naloxone HCl Human Factors Usability Studies

- **Objective and design**
  - Evaluate the usability of EVZIO and an off-label naloxone IN kit in volunteers before training and approximately 1 week after training
  - Randomized, open-label, well-controlled crossover studies
  - Opioid emergency simulation environment using a mannequin
- **Results averaged across two studies**
  - >90% of untrained users successfully administered EVZIO
  - 0% of untrained users successfully administered off-label naloxone IN kit

	Study IJ-1026SE-03O* (N=42)		Study IJ-1027SE-03O* (N=41)	
Successfully Completed Critical Tasks, n (%)	Before Training	After Training	Before Training	After Training
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%)

*kaleo sponsored studies

Kaléo's Position on Points of Discussion

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- **Opioid dependent neonates are best treated in healthcare facilities with access to titratable naloxone formulations**
- **One dose per route will avoid confusion for clinicians and patients**
- **Potential for serious risk to patients:**
  - Hesitation in prescribing or administering due to dosing confusion
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  - Real world situations that impact pharmacokinetics (e.g., common nasal medications, nasal abnormalities)

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THANK YOU.

Advisory Committee Points for Discussion Summary

1. **What should the pharmacokinetic standard be for naloxone products intended for use in the community?**

Kaléo's Position:

- The current pharmacokinetic standard (0.4 mg naloxone) has been shown historically to be a safe and effective initial dose
- Naloxone 2.0 mg:
  - Recommended for pediatrics by the American Academy of Pediatrics
  - May require fewer repeat injections during an opioid emergency involving:
    - Partial opioid agonists
    - Higher potency opioids (e.g., carfentanil-laced heroin)
- Real world situations that impact pharmacokinetics must be taken into consideration (e.g., common nasal medications, nasal abnormalities) and addressed in development and labeling

Advisory Committee Points for Discussion Summary(continued)

2. **Are there factors that support having different dose strengths and how can that be reflected in labeling to assist clinicians in product selection?**

Kaléo's Position:

- There should be one dose approved per administration route to be used in both adults and pediatrics to avoid dosing confusion for clinicians and patients
- A delay in prescribing or administering naloxone during an opioid emergency due to confusion regarding dosing is unacceptable
  - Dosing and administration for different naloxone products is already complex
  - Multiple doses per route of administration will cause even greater complexity
- Neonates who are opioid dependent are best treated in healthcare facilities (not the community setting) where there is access to naloxone formulations that can be titrated appropriately

Advisory Committee Points for Discussion Summary(continued)

3. **The current approach has been to require that naloxone products for community use are appropriate for both adult and pediatric use to minimize the risk of product confusion.**
   a. Discuss whether there should be products specifically targeting naloxone dosing for children based on the AAP recommendations.
   b. Discuss whether the standard for approval of naloxone products for use in the community should reflect pediatric dose requirements, and comment on the implications for use of these products in adults.
   c. Discuss whether it is acceptable to have different adult and pediatric products available in the home, and how to weigh the risk for product confusion.

Kaléo's Position:

- There should be one dose approved per administration route to be used in both adults and pediatrics to avoid dosing confusion for clinicians and patients
- A delay in prescribing or administering naloxone during an opioid emergency due to confusion regarding dosing is unacceptable

Advisory Committee Points for Discussion Summary(continued)

4. **There is a tension in balancing the need for rapid reversal of an opioid overdose to avoid permanent hypoxic injury to the brain and for avoiding complications from precipitated opioid withdrawal in opioid-tolerant patients. In controlled settings with adequate ventilatory support, naloxone can be titrated to effect. In the community, there is a 5 — 10 minute window before hypoxic injury is irreversible and adequate ventilatory support is often not available.**
   a. Discuss whether the Division should consider concerns of opioid withdrawal with naloxone use in the community to treat opioid overdose.

Kaléo's Position:

- Precipitation of acute withdrawal symptoms is preferable to the potentially life-threatening consequences of hypoxia
- Neonates who are opioid dependent are best treated in healthcare facilities (not the community setting) where there is access to naloxone formulations that can be titrated appropriately

Advisory Committee Points for Discussion Summary(continued)

5. **Is the pharmacokinetic standard based on 0.4 mg of naloxone given intramuscularly appropriate for approval of naloxone products for use in the community or are higher doses and/or exposures required?**

Kaléo's Position:

- The current pharmacokinetic standard (0.4 mg naloxone) has been shown historically to be a safe and effective initial dose
- Naloxone 2.0 mg:
  - Recommended for pediatrics by the American Academy of Pediatrics
  - May require fewer repeat injections during an opioid emergency involving:
    - Partial opioid agonists
    - Higher potency opioids (e.g., carfentanil-laced heroin)
- Precipitation of acute withdrawal symptoms is preferable to the potentially life-threatening consequences of hypoxia
- Real world situations that impact pharmacokinetics must be taken into consideration (e.g., common nasal medications, nasal abnormalities, etc.) and addressed in development and labeling

Advisory Committee Points for Discussion Summary(continued)

6. **As part of the standard for approval, the approved naloxone products for use in the community have Instructions for Use (IFU) suitable for use by laypersons as supported by human factors studies. The naloxone kits assembled with naloxone solution for injection and various syringe/nasal atomizer devices may have written instructions and are generally accompanied by hands on training. Discuss whether it is acceptable to approve new products intended for use in the community that require training beyond the IFU.**

Kaléo's Position:

- Approving products intended for use in the community that cannot be easily used will put patients at increased risk given the nature of an opioid emergency
- It is unlikely that the person who will be administering naloxone will receive training by the prescribing health care provider as the patient cannot self-administer
- Products need to be designed and tested to make sure they are robust, reliable and intuitive to use by non-trained individuals

BACKUPS SHOWN

Off-label kit – User Errors

- **Errors due to packaging**
  - Did not remove the atomizer from packaging
  - Did not remove the yellow cap from the injector
  - Did not remove the purple cap from the vial
  - Did not attach the atomizer to the injector
- **Errors in assembly**
  - Attached atomizer, but removed white tip
  - Attached atomizer while holding the white tip rather than the wings
  - Did not screw the vial into the injector
  - Pushed the vial into the injector and didn't release the medication
  - Drug leaked (more than a few drops) during assembly
- **Errors in usage**
  - Did not administer naloxone into either nostril
  - Administered the entire dose into one nostril

Off-label kit – User Errors

To a layperson without training the off-label kit looks like an injection device