

The Clinical Use of Naloxone

Presented By:

Joshua Lloyd, MD

Clinical Team Leader

FDA/CDER/OND

Division of Anesthesia, Analgesia, and Addiction Products

Disclaimer

The content of this talk does not necessarily reflect the views of the FDA and is entirely based on my own observations and viewpoints.

I have no potential conflicts of interest to report.

Overview of Naloxone

- Initially approved in 1971 as Narcan
- Generic injectable naloxone products are currently available
 - Labeled for intravenous, intramuscular, or subcutaneous use
 - Initial doses for opioid overdose: 0.4 mg to 2 mg
 - May repeat at 2 to 3 minute intervals
- Evzio: naloxone autoinjector
 - First naloxone product approved for use in the community
 - Approved April 2014
 - Labeled for intramuscular or subcutaneous use
 - Delivers a 0.4 mg dose

Naloxone Strengths and Presentations

- Generics to Narcan
 - **0.4 mg/ml**: Single-dose (1 ml) prefilled cartridges, ampules, and vials AND multiple-dose (10 ml) vials
 - Hospira, Mylan, International Medication Systems (Amphastar)
 - **1 mg/ml**: single-dose presentations (2 ml)
 - International Medication Systems (Amphastar)
- Evzio
 - **0.4 mg/0.4 ml**: packaged with two single-use auto-injectors and a trainer
 - Kaleo

Where is Naloxone Used?

Community Setting

- To reverse the effects of opioids
- Given via labeled routes (IM, SC) and **unapproved route (intranasal)**
- Provided in **advance** of the clinical event
 - Through a variety of risk mitigation programs, drug treatment programs, needle exchange programs and clinics to individuals with substance use disorders and to various first responders

Healthcare Setting

(e.g., EMS, ERs, Hospital inpatient)

- To reverse the effects of opioids
- Given via labeled routes (IV, IM, SC)
- Provided **at the time** of the clinical event

The Indication for Evzio Encompasses Use in Community Settings

Generic Naloxone

- Complete or partial reversal of opioid depression, including respiratory depression, induced by opioids
- **Diagnosis** of suspected acute opioid overdose
- May be useful as an adjunctive agent to increase blood pressure in the management of **septic shock**

Evzio

- The emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression
- Intended for immediate administration as **emergency therapy in settings where opioids may be present**
- **Not a substitute for emergency medical care**

Intranasal Use in the Community

- Unapproved route of administration
- Provided in a kit containing
 - Naloxone for injection (1 mg/ml)
 - Luer lock syringe barrel
 - Mucosal atomizer device (MAD)
- Half of the volume (~1 ml) sprayed in one nostril and remaining volume sprayed in other nostril



FDA Approach to New Formulations of Naloxone

- FDA recognizes the public health imperative that naloxone be available in any setting where opioids may be present and, therefore, where there is potential for overdose
- FDA outlined a pathway for new formulation development at the 2012 public workshop

Approach to New Formulations of Naloxone: Standard of Approval

- FDA has described a pharmacokinetic standard for new formulations of naloxone in lieu of conducting efficacy studies
 - Ethical challenges associated with conducting efficacy studies in this clinical setting
 - Can conduct a relative bioavailability study in normal healthy volunteers
 - Must match or exceed the pharmacokinetic profile of naloxone via an approved route of administration, particularly in the early critical period (i.e., from time of administration to the peak plasma concentration for naloxone by the approved route)

FDA Review of New Formulations of Naloxone: Past, Present, and Future

- Review of Evzio
 - Conducted an expedited review of the Evzio application culminating in approval 2 months ahead of the 6-month PDUFA goal date
- Review of intranasal formulations under development
 - FDA has utilized expedited programs for intranasal formulations of naloxone that are currently under development, where applicable
- Review of future formulations
 - FDA will continue to expedite the review of naloxone products that address an unmet medical need and/or would provide a significant improvement in safety or effectiveness