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

INSYS Therapeutics, Inc.
Phoenix, AZ

INSYS
THERAPEUTICS, INC.

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Naloxone Meeting

October 5, 2016

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Disclosures:

- I am an employee of Insys Therapeutics, Inc.

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Insys Therapeutics, Inc

An innovative organization, passionate about our mission to make a difference in the lives of patients and set new standards with our products

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Naloxone

- Opioid overdose – heroin and Rx opioids
- Alternative Routes of Administration
  - Current routes of administration and their limitations
  - Barriers to adequate administration
  - Potential Solutions
- Dose
- Onset
- Pediatrics

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Naloxone - Alternative Routes of Administration

- First approved for intravenous, intramuscular, and subcutaneous injection, with IV the recommended route
- Many patients needing naloxone are injection drug users, 80% of whom are Hep C or HIV positive
- Venous access may be difficult or impossible in chronic IV drug users
- Unmet medical need - Easy to use devices with lay-friendly instructions that eliminate the risk of needle-stick injury are imperative
- Expanding access to those who are in close contact is critical
- Intranasal device was recently approved

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Naloxone – Limitations of Current Routes of Administration

- 17% of subjects who received intranasal naloxone were unresponsive, but responded to IV
- Nasal defects may impact response to intranasal naloxone
  - Repeated use of cocaine or other opioids through the nose can cause destruction, scarring, perforation, loss of tissue and necrosis of the nasal septum, nasal mucosa, and associated naso- and oropharyngeal tissues
- Contraindications to intranasal administration include:
  - Nasal septal abnormalities
  - Nasal trauma
  - Epistaxis
  - Excessive nasal mucus
  - Intranasal damage caused by substance abuse
- Nasal congestion due to colds or allergic conditions may interfere with drug delivery
- **Other easy-to-use, non-invasive, less expensive alternatives are still needed**

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Naloxone - Alternative Routes of Administration

- Death is usually caused by severe respiratory depression that can be prevented by timely administration of naloxone
- Respiratory depression, which is reversible until death occurs, can take 1 to 3 hours and can be reversed
- The most important thing is to act right away
- A barrier to greater community use is a suitable and optimized needle free drug delivery system

Sublingual route of administration could be used in patients:

- Who are awake but unable to speak
- May be out of it, but respond to outside stimulus like a loud noise or a light shake

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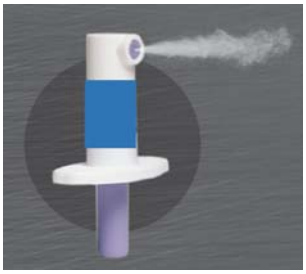
Naloxone – Alternative Route of Administration

Easy to use sublingual device



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Naloxone - Alternative Routes of Administration

- Sublingual route of administration resulted in levels higher than IM at 2, 4, 6, 8, and 10 minutes
- The ratios of mean plasma concentrations are higher relative to the 0.4 mg IM.
- The ratios for Naloxone 8mg administered sublingually range from 1.2-fold to 3.3-fold higher from 2 minutes through 1 hour post-dose compared to 0.4 mg IM dose
- Both treatments were generally well tolerated

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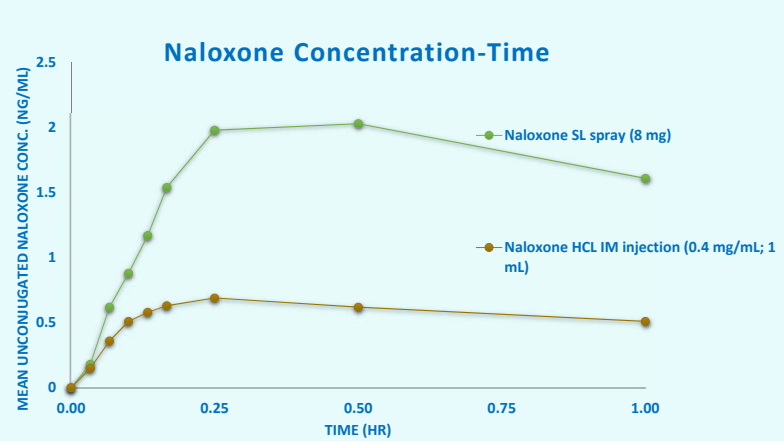
Naloxone Comparative Trial



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Naloxone - Onset

- Treatment must begin as early as possible, before the EMTs arrive
- IV administration provides rapid and relatively higher exposure vs other routes but may not be as well tolerated or not as easy to administer by a lay person
- IV has an onset within 1-2 minutes and IM within 2-5 minutes
- Intranasal and sublingual routes should be expected to demonstrate PK levels comparable to IM levels within 2 minutes

New drug products and alternative routes should be required to match IM levels at 2 minutes

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Naloxone - Dose

- Initial dose for suspected overdose is 0.4 to 2 mg, which may be repeated to a total dose of 10 mg
- Extremely high doses (up to 5.4 mg/kg boluses and 4 mg/kg/h infusion) have been administered without any reported AEs
- Dose and route produce variable intensity of AEs and withdrawal symptoms – IV and higher doses produce more AEs and more severe withdrawal symptoms
- Withdrawal symptoms are transient and do not impact the use of higher doses
- Clinical trials in opioid overdose setting are unethical and unwarranted provided the high safety margin with current doses

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Naloxone - Pediatrics

- Neonates – insufficient evidence to evaluate the safety and efficacy of administering naloxone to a new born with respiratory depression due to maternal opiate exposure (AAP)
- Pediatric studies would not be feasible
- For non-invasive devices, the adult dose is acceptable in children as AEs are generally tolerable and the risk/benefit ratio is positive

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Naloxone - Recommendations

- Sublingual and other alternative delivery devices should be considered for the delivery of naloxone
- Demonstrated levels exceeding IM at 2 minutes should be required
- Adult doses in single use devices should be acceptable in pediatrics
- Development of a device that can be used intranasally or sublingually should be encouraged

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Thank you, any questions?

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