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

Amphastar Pharmaceuticals
Rancho Cucamonga, CA

AMPHASTAR
PHARMACEUTICALS

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

Intranasal Naloxone

Intended for Use in the Community

Amphastar Pharmaceuticals, Inc.

October 5, 2016

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

Part A
Introduction

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President

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October 5, 2016

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Agenda

Part A	**Introduction**	**Jason Shandell, J.D., M.B.A., Esq.** President Amphastar Pharmaceuticals, Inc.
Part B	**Intranasal Off-Label Use of IMS Naloxone Injection (2mg/2mL) by Overdose Prevention Programs**	**Tony Marrs, MPH** VP, Clinical Operations, Amphastar Pharmaceuticals, Inc.
Part C	**Development of Intranasal Naloxone**	**Robert Cormack, Ph.D.** Senior Director, Regulatory Affairs Amphastar Pharmaceuticals, Inc.

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Naloxone for Opioid Overdose Reversal

- Overdose Prevention Programs distributing naloxone started as far back as 1996 [1]
- Opioid overdose has become a major public health crisis: From 1999 to 2014, more than 165,000 people have died in the U.S. from overdoses related to prescription opioids. [2]
- Intranasal (IN) naloxone is highly effective due to the large and highly vascularized area of the nasal airway, which allows for fast absorption
- Reported clinical evidence and multi-state survey data regarding IN naloxone use demonstrate that IN administration is safe and highly effective for opioid overdose reversal

[1] Centers for Disease Control and Prevention (CDC). Community-based opioid overdose prevention programs providing naloxone - United States, 2010. MMWR Morb Mortal Wkly Rep. 2012 Feb 17;61(6):101-5.

[2] Centers for Disease Control and Prevention. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics, 2016.

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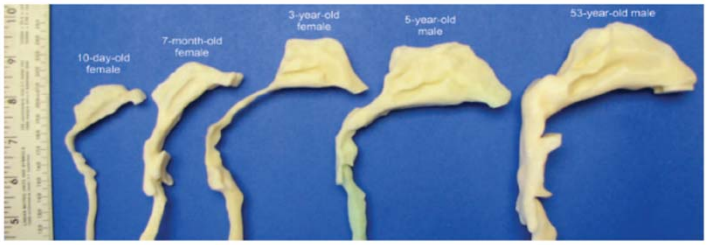
Intranasal: A Highly Effective Delivery Method

Nasal Airway Volume and Surface Area [1]

10 days, F 7 Months, F 3 Years, F 5 Years, M 53 Years, M



Age & Gender	10 Day-old Female	7 Month-old Female	3 Year-old Female	5 Year-old Male	53 Year-old Male
Total Nasal Airway Volume (cm^3, mL)	3.51	10.33	13.32	22.21	55.05
Total Nasal Airway Surface Area (cm^2)	38.09	76.73	106.85	168.14	256.01

[1] Xi J, Si X, Zhou Y, Kim J, Berlinski A. Growth of nasal and laryngeal airways in children: implications in breathing and inhaled aerosol dynamics. Respir Care. 2014 Feb;59(2):263-73.

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Desired Features of Intranasal Naloxone

Compared to naloxone injection (IM), reformulated intranasal naloxone should provide for:

- **Efficacy, with Quick Onset**: Comparable or higher partial-time naloxone concentration as compared to 0.4-mg IM dose
- **Safety profile**: Same or less total systemic exposure as compared to 2 mg IM;
- Ease of use for both medical professionals and lay persons, as demonstrated in human factor studies;
- No introduction of meaningful side effects, such as local irritation or Acute Withdrawal Syndrome (AWS);
- Administration into one nostril, with a second unit that is readily available, if needed.

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Part B

Intranasal Off-Label Use of IMS Naloxone Injection (2mg/2mL) in Overdose Prevention Programs

Tony Marrs, MPH
Vice President, Clinical Operations

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October 5, 2016

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Intranasal IMS Naloxone (2mg/2mL) Case Study: A Retrospective Analysis

Case Study – NY and NJ Overdose Prevention Programs

- Drug: IMS naloxone injection 2 mg/2 mL, off-label by IN
- Setting: First responders in community
- Data Sources*
  - New York State Public Safety Naloxone Quality Improvement Usage Reports
  - NJ Attorney General's Heroin & Opiates Task Force: Naloxone Deployment Reporting Form

* Used with permission from Offices of Attorney General of New York and New Jersey in relation to the naloxone kits that have been purchased through Community Overdose Prevention (COP) funding under NY and NJ COP Programs.

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Intranasal IMS Naloxone (2mg/2mL) Case Study: Demographics and Treatment Characteristics

- 1,765 treated victims, 1,390 identified* as opioid overdose population (OOP)
- In OOP:
  - Age: Average 31 years
  - Gender: 70% male, 30% female
  - Race: 65% Caucasian
  - Average naloxone doses used:
    - 65% – 1 unit: 2 mg IN
    - 33% – 2 units: 2 × 2 mg IN
    - 2% – 3 or more units: ≥ 3 × 2 mg IN

* Identified by first responders in NY and NJ.

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Intranasal IMS Naloxone (2mg/2mL) Case Study: Significant Findings in Survival

- Overall survival rate: 93.9% (n=1,390)
- Response time: 84% within 5 minutes
- 98% required only 1 or 2 units to reverse
  - Average 1.4 units used
- Reported fentanyl overdose reversal:
  - 8 cases
  - 100% survival rate
  - Average of 1.5 units used

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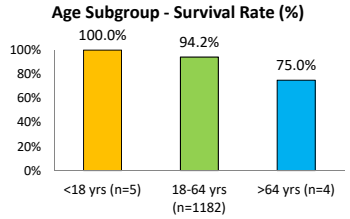
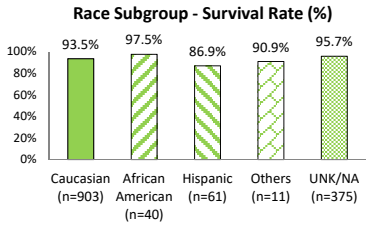
Intranasal IMS Naloxone (2mg/2mL) Case Study: Age and Race Survival Rate (SR) Analyses

Age



Race



- **By age:**
  - <18 yrs, SR=100% (n=5)
  - 18-64 yrs, SR=94.2% (n=1,182)
  - ≥65 yrs, SR=75% (n=4)
- **By race:**
  - Caucasian: SR=93.5%
  - African American: SR=97.5%
  - Hispanic: SR=86.9%
  - Others: SR=90.9%
  - Unknown: SR=95.7%

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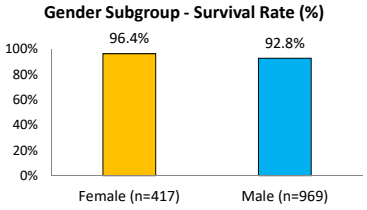
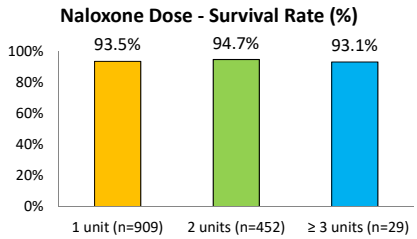
Intranasal IMS Naloxone (2mg/2mL) Case Study: Gender and Dose Survival Rate Analyses

Gender



Naloxone Dose



- **By gender:**
  - Male: SR = 92.8% (n=969)
  - Female: SR = 96.4% (n=417)
- **By naloxone dose:**
  - 1 unit (2 mg): SR=93.5% (n=909)
  - 2 units (2 × 2 mg): SR=94.7% (n=452)
  - 3 or more units (≥3 × 2 mg): SR=93.1% (n=29)

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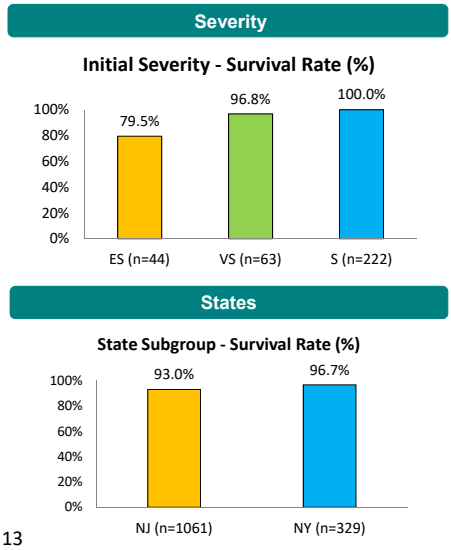
Intranasal IMS Naloxone (2mg/2mL) Case Study: Severity and State Survival Rate Analyses



- **By initial severity status:**
  (NY only)
  - **Extremely Severe (ES)**:
    No breathing and no pulse:
    SR=79.5% (n=44)
  - **Very Severe (VS)**:
    No breathing or no pulse:
    SR=96.8% (n=63)
  - **Severe (S)**:
    Slow breathing and/or slow pulse:
    SR=100% (n=222)
- **By state:**
  - NJ: SR=93.0% (n=1061)
  - NY: SR=96.7% (n=329)

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Intranasal IMS Naloxone (2mg/2mL) Case Study: Conclusions

- What can be learned from the data?
  - Findings:
    - Significant opioid overdose reversal rate (93.9%, n=1,390)
    - A majority of victims responded within 5 minutes (84%)
  - Subgroup analysis of data for naloxone dose:
    - 98% of victims received 1 (2 mg) or 2 units (2 × 2 mg) of intranasal naloxone (2 mg/2 mL)
    - Therefore, a two-unit kit is necessary and appropriate
  - IN naloxone (2 mg/2 mL) is safe and effective

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Part C

Development of Intranasal Naloxone

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Amphastar Pharmaceuticals, Inc.

October 5, 2016

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Intranasal Naloxone Development: Product and Configuration

- Emergency-ready device: allows rapid delivery
- Demonstrated stable when stored at temperature extremes (2°–40°C)
- Sterile solution
- Preservative-free
- Single-nostril delivery
- Demonstrated to be effective at multiple victim head/neck positions
- Two units per package

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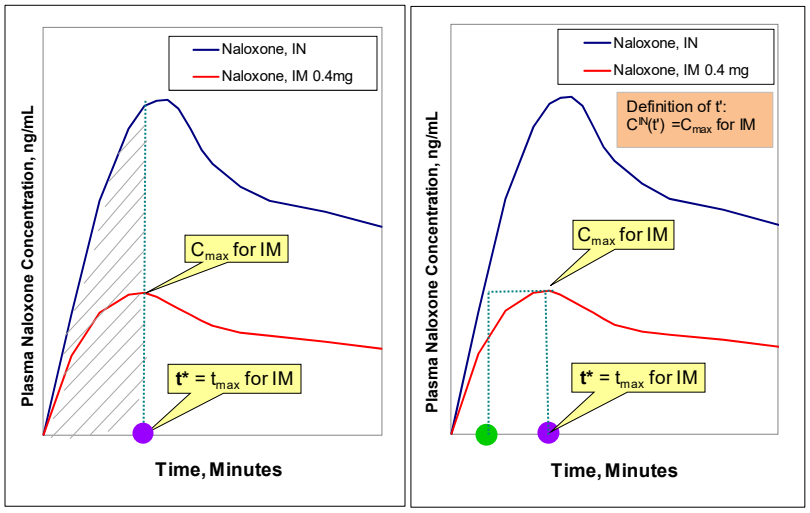
Intranasal Naloxone Development: Pharmacokinetics

Efficacy Assessment: AUC $_{0\text{-}t^*}$ **Onset Time Assessment: t'**



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Intranasal Naloxone Development: Assessment of Efficacy and Onset

To meet the efficacy evaluation for approval

- **Efficacy:** Comparable or higher naloxone exposure at t* (the t_{max} of the RLD, 0.4 mg IM) characterized by $AUC_{0\text{-}t^*}$
- It should be expected

Efficacy:	**Proposed Naloxone IN Product**	>	**IMS Product (2mg/2mL) by IN**	>	**Naloxone 0.4 mg by IM**

- **Onset Time**: Not delayed, characterized by t′.

$$C^{IN}(t') = C_{max}^{IM,\ 0.4\ mg}$$

Onset:	**Proposed Naloxone IN Product**	<	**IMS Product (2mg/2mL) by IN**	<	**Naloxone 0.4 mg by IM**

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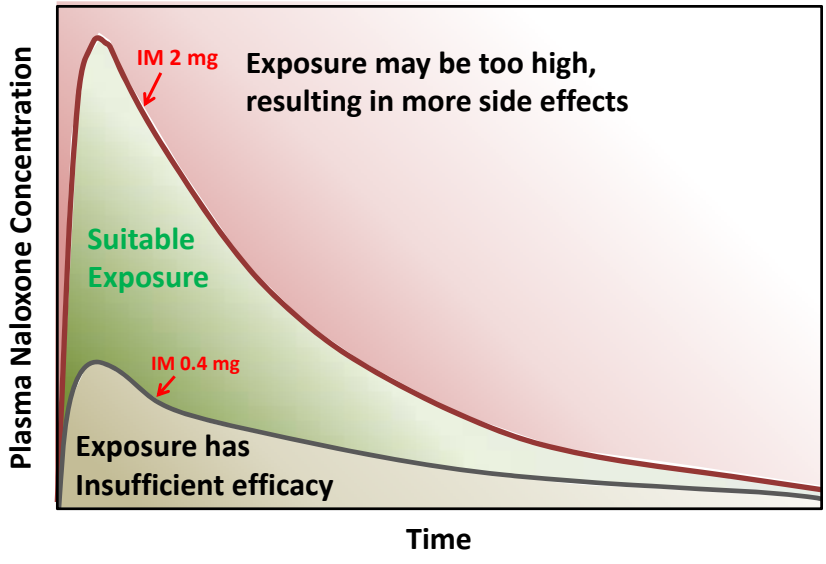
Intranasal Naloxone Development: Optimal Dose Zone



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Intranasal Naloxone Development: Proposed Safety Evaluation

Systemic Exposure

- Should not exceed the total systemic naloxone exposure for 2 mg IM (based on AUC_{0-inf})

Local Tolerability

- Nasal and oropharyngeal mucosa examination
- Subject symptom self-assessment
- Important for high-dose formulations (such as 10 × of the highest concentration of the FDA-approved injectable naloxone)

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Intranasal Naloxone Development: Proposed Safety Evaluation (cont'd)

Assessment of Acute Withdrawal Syndrome (AWS)

- AWS important for high-dose formulations (exceeds the highest approved single dose for naloxone injection)
- "Dope sick"
- "Abrupt reversal of opioid effects …has precipitated an acute withdrawal syndrome. Signs and symptoms have included: body aches, fever, … restlessness or irritability, …tachycardia."[1]
- Vomiting
- Creates a risk of injury to first responders or bystanders
  - Affects willingness to administer product

[[1]] Package insert for Evzio (naloxone for injection)

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Intranasal Naloxone Development: Human Factors Study

- Human factors study should be required to optimize labeling as well as design of the device
- Key features
  - Intended users of IN naloxone
    - First responders (EMTs, police officers)
    - Laypersons (non-medically trained)
    - Adolescents
  - Stressful testing environment
- Validate successful understanding of the labeling for the intended user populations

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