

JOINT BRIEFING NOTE ON BEHALF OF ADAPT PHARMA (A SUBSIDIARY OF EMERGENT BIOSOLUTIONS), KALEO AND INSYS THERAPEUTICS NALOXONE CO- PRESCRIBING NOVEMBER 2018

Opioid Overdoses: A National Public Health Epidemic Impacting Local Communities

As a leading cause of preventable injury and death, opioid overdose is a major contributor to worsening overall survival among middle-age white Americans and an increasing cause of mortality among all racial and age categories.¹ Death from opioid overdoses is a growing epidemic in the United States, with poisoning deaths involving opioid analgesics having more than tripled in the United States since 1999. Drug overdoses killed 63,632 persons in 2016 and are predicted to have exceeded 72,000 in 2017, with some apparent levelling off.²

In 2016, nearly two-thirds of deaths in 2016 (66%: 42,249 persons) involved a prescription or illicit opioid. Overdose deaths increased in all categories of drugs examined for men and women, people ages 15 and older, all races and ethnicities, and across all levels of urbanization. Overdose deaths involving illicit opioid overdose have risen rapidly in recent years, particularly those involving synthetic opioids such as illicitly manufactured fentanyl.³

Prescription Opioids Play a Central Direct and Indirect Role in Overdose Deaths

Prescription opioids continue to play a critical direct and indirect role in opioid overdose mortality. CDC research estimate that in 2016 prescription opioids were involved in 40% of opioid overdose deaths.⁴ Prescription opioid deaths are widespread across the United States and are not confined to a select number of geographic locations. Data also suggest that non-medical prescription opioid use often precedes illicit opioid use. In the period 2008–2010, 82.6% of frequent nonmedical users who used heroin in the past year reported nonmedical use of opioid pain relievers prior to heroin initiation.⁵ CDC 2016 data estimate that 11.5 million Americans self-reported misusing prescription pain relievers in the previous 12 months.⁶

Naloxone Hydrochloride can Reverse Opioid Overdose Symptoms

Naloxone hydrochloride is an opioid-receptor antagonist, with evidence indicating high affinity for μ -opioid receptors. It was first approved in injectable form by Food and Drug Administration (FDA) in 1971 (NDA 16-636) for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids including propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine and butorphanol and cyclazocine. Naloxone hydrochloride is also indicated for the diagnosis of suspected or known acute opioid overdosage.⁷

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Most opioid overdose deaths happened outside medical facilities (75%) most frequently in the decedent's homes (53%).⁸ This facet of the opioid crisis led to the development and subsequent FDA approval of two naloxone products intended for use outside medical facilities by non-medically trained persons: Emergent BioSolutions' (formerly Adapt Pharma) **Narcan[®] Nasal Spray** was approved in 2015 and Kaléo's **Evzio[®] auto-injector** was approved in 2014. Both of these 'community use' products are (i) indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression; (ii) intended for immediate administration as emergency therapy in settings where opioids may be present; and (iii) are not substitutes for emergency medical care. In addition, at least one additional company, Insys Development Company, Inc., is developing a naloxone nasal spray and it has reported publicly its plans to submit a New Drug Application (NDA) in 1Q2019.

The Criticality of Rapidly Expanding Access to Naloxone

The opportunity to intervene and potentially treat an opioid overdose with community use naloxone products is significant. A recent CDC analysis of 11,884 opioid overdose deaths across 11 States in the year ended June 2017, indicate bystanders were present in about 40% of deaths but naloxone was rarely administered.⁹ Ensuring the availability of community use naloxone products at the place and time of overdose is critical. Indeed, better targeting the availability of lifesaving overdose-reversing drugs is one of five Strategies the U.S. Department of Health and Human Services (HHS) is pursuing to combat the opioid crisis.¹⁰

CDC Guideline for Prescribing Opioids for Chronic Pain

In March 2016, CDC released the **CDC Guideline for Prescribing Opioids for Chronic Pain** (CDC Guideline) to ensure that patients have access to safer, more effective chronic pain treatment, while reducing the number of people who misuse opioids, develop opioid use disorder, or overdose. The Guideline focused on the prescribing of opioid pain medication to patients 18 years and older in primary care settings outside of active cancer treatment, palliative care and end of life care.

The CDC Guideline makes a total of 12 recommendations including the following recommendation 8 relating to safety and risk-mitigation:

"Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when

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factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (=50 MME/day), or concurrent benzodiazepine use, are present.”

This recommendation reflected the relatively higher odds of opioid overdose associated with higher opioid dosages; concurrent benzodiazepine use; and prior overdose or substance use disorder. For example, in four studies, compared with opioids prescribed at <20 MME/day, the odds of overdose among patients prescribed opioids for chronic nonmalignant pain were between 1.3 and 1.9 for dosages of 20 to <50 MME/day, between 1.9 and 4.6 for dosages of 50 to <100 MME/day, and between 2.0 and 8.9 for dosages of \geq 100 MME/day.¹¹

Additionally, in August 2016, FDA announced it was requiring a class-wide safety update for opioid products adding a Boxed Warning that the concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.¹²

Co-Prescribing Naloxone as a Policy is Broadly Supported

Beyond CDC's recommendation that clinicians consider co-prescribing naloxone alongside higher risk prescriptions to mitigate risk, co-prescribing naloxone is broadly supported by the medical community, federal and state health bodies, advocacy groups. Examples include:

The National Academies of Sciences, Engineering and Medicine (NAS) Pain Management and the Opioid Epidemic Report (Recommendation 5-9)¹³; American Medical Association (AMA); the AMA Opioid Task Force of 26 national and state medical Societies¹⁴; American Society of Addiction Medicine (ASAM); Substance Abuse and Mental Health Services Administration (SAMHSA); Federation of State Medical Boards; Vermont Department of Health; Maryland Department of Health and Mental Hygiene; Rhode Island Department of Health; World Health Organization (WHO); FDA in its Consumer Update¹⁵; National Institutes on Drug Abuse (NIDA); US Department of Veteran's Affairs; Partnership for Drug Free Kids; Harm Reduction Coalition; Caregiver Action Network; Young People in Recovery; and Facing Addiction.

FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain was updated in September 2018 and includes as one of the goals of its educational effort for Health Care Providers

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“HCPs will also become familiar with the use of naloxone and with the importance of its availability for use by patients and caregivers both in the community and in the home.”¹⁶

In April 2018, the Office of the Surgeon General issued the following advisory advocating expanding naloxone access to patients taking high doses of opioids:

“I, Surgeon General of the United States Public Health Service, VADM Jerome Adams, am emphasizing the importance of the overdose-reversing drug naloxone. For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, knowing how to use naloxone and keeping it within reach can save a life.”¹⁷

In an ambulatory clinic setting, current practice guidelines suggest that healthcare providers should screen patient’s aberrant drug-related behaviors. Provided the difficulty of predicting which patients on chronic opioid therapy will experience opioid overdose, a new paradigm of harm reduction is called for. If naloxone is co-prescribed in a Universal Precautions manner for all patients receiving chronic opioid therapy, it may have a significant impact on intentional and unintentional opioid overdose deaths. Takeda et al. demonstrated that ambulatory co-prescribing of naloxone in a Universal Precautions model for all patients can be adopted as a useful public health intervention.¹⁸

Experience with Co-Prescribing Naloxone has been Favorable

Medical providers are in an ideal position to prescribe take-home naloxone to reduce the number of overdose deaths among their patients. Primary care providers and patients have generally found co-prescribing naloxone acceptable and that co-prescribing does not increase liability risk.^{19,20,21}

The VA implemented a system wide opioid initiative, including naloxone prescribing broadly consistent with the CDC guideline, and achieved a 26% drop in VA patients prescribed opioids, 60% reduction in opioid/ benzodiazepines and a 39% reduction in veterans on long term opioid treatment.²²

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One of the earliest efforts in naloxone co-prescription was made by Project Lazarus I Wilkes County, North Carolina, which saw a 70% decrease in prescription opioid-related overdose death rates during the implementation phase of the project.²³

Coffin et al. in a study funded by NIDA, conducted a non-randomized intervention study of naloxone co-prescription for primary care patients on long-term opioid therapy for pain. This study was designed to evaluate the feasibility and impact of implementing naloxone prescriptions to patients prescribed opioids for chronic pain. The results of this study found that receipt of naloxone was independently associated with a 63% reduction in opioid-related ED visits after one year, raising the possibility that providing naloxone impacted patient behavior with respect to opioids.²⁴

Improving prescriber knowledge about community naloxone programs and prescribing naloxone may help distribute naloxone more broadly, especially in communities that do not have access to an opioid overdose and education and community naloxone distribution (ONED).¹ Access through traditional medical and pharmacy settings may offer some advantages to obtaining naloxone including scale and insurance coverage.²⁵

Contrasting Adoption of Naloxone Co-Prescribing

Notwithstanding the publication of the CDC Guideline and the widespread support for naloxone co-prescribing, at a national level in 2017 there were less than 8 naloxone prescriptions dispensed for every 1,000 opioid prescriptions of at least 50 Morphine Milligram Equivalent (MME) dispensed. In contrast, five States Virginia (Board of Medicine), Vermont (Department of Health), Arizona (Medical Association), Rhode Island (Department of Health) Florida (Florida Health HB 21) introduced regulations requiring naloxone to be prescribed or offered when certain criteria are met. Similar regulation requiring naloxone prescribing will become effective in Washington State in November 2018 and in California in January 2019. While the specific criteria triggering the requirement differ by State, most mirror some or all of the CDC Guideline recommendations of (i) concurrent opioid / benzodiazepine use; (ii) history of substance or opioid use disorder or past overdose; (iii) higher opioid dosage but at a various MME thresholds of 120 MME (VA), 90 MME (VT, AZ), 50 MME (RI) and trauma injury with an injury severity score of 9 or more (FL).

When naloxone co-prescribing is a requirement, naloxone distribution levels are dramatically different. For example, in Virginia in 2017 the number of naloxone prescriptions dispensed for every 1,000 opioid prescriptions of at least 50 Morphine Milligram Equivalent (MME) was 5 times higher than the national average.

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Importantly, the implementation of these State level regulations provide a proxy for the demand side implications of a national naloxone prescribing regulatory action. In each state, the introduction of the regulation resulted in an immediate spike in demand – a key consideration for any federal / national co-prescribing regulatory action.

Absent a national policy to accelerate adoption, it is anticipated that naloxone distribution will expand at a slower rate and that criteria triggering a naloxone co-prescription will continue to vary by regulatory body. Therefore, a FDA action rooted in safe prescribing of opioids would accelerate targeted and consistent prescribing of naloxone alongside opioids carrying the greatest risk of overdose.

FDA Regulatory Options for Co-Prescribing Action

The statutory authority to require the prescribing of naloxone alongside high-risk opioids or to at-risk persons, in order to potentially treat an opioid overdose, is inherent in FDA's ability to approve the "conditions of use" of a prescription medicine and is further supported by the amendments to the Federal Food, Drug, and Cosmetic Act that created new safety authorities, including REMS.

FDA has compelled the co-prescription of second medications when necessary to create or support either the safety or effectiveness of a drug. For example, FDA has already acknowledged the risk of fentanyl by making recommendations within professional prescribing information to have an antidote available when an intravenous form of the drug is administered. There is also precedent for FDA to require medical interventions to assure safe use – e.g., clozapine blood monitoring prior to clozapine prescription dispensing.

In this case, a warning and prescribing intervention are necessary because a medical intervention is required to be executed prior to dispensing the opioid to the patient – namely the co-prescribing of naloxone. This prescribing requirement is intended to reduce the serious and potentially fatal risk associated with the use, misuse or abuse of specified opioid prescriptions and the risk of opioid overdose following relapse for those receiving a prescription for opioid dependency.

Such a prescribing intervention would not be unduly burdensome as it could be implemented using existing prescribing, distribution and reimbursement channels. Moreover, by targeting

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the requirement at those opioids that carry the greatest risk of overdose, the requirement would be commensurate with the serious identified risk.

Regulatory Considerations:

Mechanism: Regulatory options available to FDA include (i) a Class Wide Safety Update or other modification to Opioid Labels with a communication plan to HCPs; and (ii) an additional Element to Assure Safe Use (ETASU) to the Opioid REMs

Criteria for co-prescribing: Options include (i) opioid and benzodiazepine concurrent use; and (ii) a substance or opioid use disorder diagnosis or past overdose; and (iii) opioid dosages (all dosages, >50 MME, >90 MME. >120 MME).

Implementation Timeframe: FDA could consider an appropriate lead-in time or phased introduction to allow for implementation of the regulatory changes and the production and capacity build such an action could generate.

Presenting Sponsor will provide their respective recommendations and perspective on the demand, supply, and cost implications of these regulatory options.

1 Kerensky T and Walley YW, *Opioid overdose prevention and naloxone rescue kits: what we know and what we don't know*, *Addict Sci Clin Pract* (2107) 12:4. DOI 10.1186/s13722-016-0068-3

2 Ahmad FB, Rossen LM, Spencer MR, Warner M, Sutton P. *Provisional drug overdose death counts*. National Center for Health Statistics. 2018

3 CDC Press Release March 29 2018: *U.S. drug overdose deaths continue to rise; increase fueled by synthetic opioids* Access November 2018 at <https://www.cdc.gov/media/releases/2018/p0329-drug-overdose-deaths.html>

4 Seth P. *Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants — United States, 2015–2016*. *MMWR Morb Mortal Wkly Rep* 2018;67:349–358.

5 Jones CM. *Drug Alcohol Depend. Sep 2013 Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers – United States, 2002–2004 and 2008–2010*

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6 Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. Surveillance Special Report. Published August 31, 2018. Accessed October 2018 from <https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf>

7 NIH Daily Med naloxone hydrochloride injection
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=236349ef-2cb5-47ca-a3a5-99534c3a4996>

8 CDC Wonder Database 2016. Accessed October 2018.

9 Mattson CL Morbidity and Mortality Weekly Report (MMWR). Centers for Disease Control and Prevention. <https://www.cdc.gov/mmwr/volumes/67/wr/mm6734a2.htm>. Published August 30, 2018

10 HHS 5-Point Strategy To Combat the Opioid Crisis. Available at <https://www.hhs.gov/opioids/about-the-epidemic/hhs-response/index.html>

11 CDC Guideline for Prescribing Opioids for Chronic Pain
<https://www.cdc.gov/drugoverdose/prescribing/guideline.html>

12 FDA Press Release August 31 2016. FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use. Available at <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm518697.htm>

13 The National Academies of Sciences, Engineering and Medicine (NAS) Pain Management and the Opioid Epidemic Report Available: <https://www.nap.edu/download/24781#>

14 The AMA Task Force members include: American Academy of Addiction Psychiatry; American Academy of Family Physicians; American Academy of Hospice and Palliative Medicine; American Academy of Orthopaedic Surgeons; American Academy of Pain Medicine; American Academy of Pediatrics; American Academy of Physical Medicine and Rehabilitation; American Association of Neurological Surgeons and Congress of Neurological Surgeons; American College of Emergency Physicians; American College of Occupational and Environmental Medicine; American College of Physicians; American Congress of Obstetricians and Gynecologists; American Dental Association; American Medical Association; American Osteopathic Association; American Psychiatric Association; American Society of Addiction Medicine; American Society of Anesthesiologists; Arkansas Medical Society; California Medical Association; Massachusetts Medical Society; Medical Society of the State of New York; New Mexico Medical Society; Ohio State Medical Association; Oregon Medical Association; and Utah Medical Association.

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15 FDA Consumer Update “What to Ask Your Doctor Before Taking Opioids?” Accessed October 2018 at: <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm529517.htm>

16 FDA’s Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain. Available at: <https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM620249.pdf>

17 Office of the Surgeon General; US Department of Health and Human Services. Surgeon General’s Advisory on Naloxone and Opioid Overdose. Available at <http://www.surgeongeneral.gov>.

18 Takeda MY, Katzman JG, Dole E, Bennett MH, Alchbli A, Duhigg D, Yonas H. Co-prescription of naloxone as a Universal Precautions model for patients on chronic opioid therapy-Observational study. *Subst Abus.* 2016 Oct-Dec;37(4):591-596. Epub 2016 Apr 19.

19 Behar, Rowe et al, “Primary Care Patient Experience with Naloxone Prescription”, *Annals of Family Medicine*, September 2016.

20 Behar, Rowe et al, “Acceptability of Naloxone Co-Prescription Among Primary Care Providers Treating Patients on Long-Term Opioid Therapy for Pain”, *Journal of General Internal Medicine*, November 2016.

21 Davis, Burris et al, “Co-prescribing Naloxone Does Not Increase Liability Risk”, *Journal of Substance Abuse*, October 2016.

22 Federal Healthcare System Experience: VA Implementation, Maintenance, and Evaluation C. Bernie Good MD, MPH Veterans Affairs Pharmacy Benefits Management May, 2017. Available at <https://www.fda.gov/downloads/Drugs/NewsEvents/UCM558389.pdf>

23 Albert S, Brason FW, 2nd, Sanford CK, Dasgupta N, Graham J, Lovette B. Project Lazarus: community-based overdose prevention in rural North Carolina. *Pain Med.* 2011;12 Suppl 2:S77-85. doi: 10.1111/j.1526-4637.2011.01128.x.

24 Coffin, Behar et al, “Nonrandomized intervention of Naloxone Co-prescription for Primary Care Patients Receiving Long Term Opioid Therapy for Pain”, *Annals of Internal Medicine*, 20 August 2016.

25 Mueller et al., A review of Opioid Overdose Prevention and Naloxone Prescribing: Implications for Translating Community Programming into Clinical Practice, *Subst Abus.* 2015;36(2):240-253. doi:10.1080/08897077.2015.1010032.

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FDA Advisory Committee

December 17 & 18 2018

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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Agenda

- About Emergent BioSolutions
- About Naloxone and Narcan Nasal Spray
- Key Points from Sponsor Joint Co-prescribing Briefing Document
- Estimating Population on Higher Risk Opioids and Adoption
- Impact of State Regulations on Narcan Nasal Spray Adoption
- Estimating Impact of FDA Regulatory Action on Adoption
- Dynamics Influencing Access and Affordability
- Capacity and Cost
- Recommendation

About Emergent BioSolutions

Emergent BioSolutions Acquired Adapt Pharma Including Narcan® (naloxone) Nasal Spray in 4Q18

Global Life Science Business Focused on Public Health Threats

- Significant scale: NYSE Listed; 1,600 employees; 19 global locations
- 11 Products and 7 Projects in Clinical Development
- Portfolio includes vaccines such as BioThrax® (anthrax vaccine); ACAM2000® (smallpox vaccine)

Supporting Expanded Access to Narcan Nasal Spray

- Leverage Emergent's two decades of expertise addressing public health threats
- Maintain affordable access for public health purchasers, health insurance systems and individuals
- Investing in supply chain capacity, awareness and pipeline

 **NARCAN**® (naloxone HCl)
NASAL SPRAY 4mg

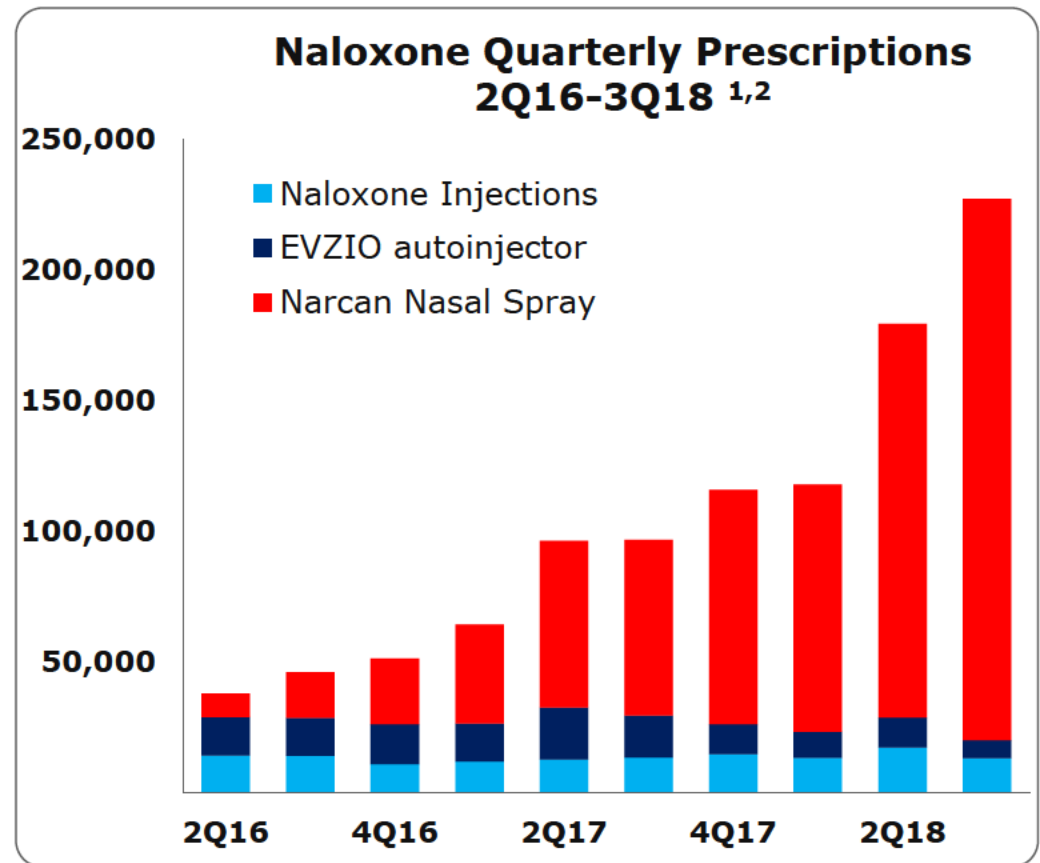
About Naloxone and Narcan Nasal Spray

Naloxone Prescriptions are Growing

- Narcan accounts for **>90%** of prescriptions
- Growth driven by affordability, accessibility and awareness

Narcan 4mg Nasal Spray

- FDA-approved for community use
- Each device delivers a 4mg/0.1 ml spray
- Supplied in carton with 2 devices
- Product shelf-life is 2 years



1. Prescription Data only which excludes all units shipped to Public Health 2. IQVIA Prescription Database

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Key Points from Briefing Documents

Prescription Opioids Continue to Play a Key Role in Crisis

- 40% of opioid overdose deaths involve prescription opioids¹
- Most who use illicit opioids, first misused prescription opioids²
- 40% of opioid overdoses are witnessed, but naloxone is rarely administered³

Co-prescribing Naloxone is Widely Endorsed but Narrowly Adopted

- CDC Opioid Guideline identifies opioid prescriptions associated with higher risk of opioid overdose⁴
- Co-prescribing naloxone with these prescriptions is endorsed by multiple opioid crisis stakeholders⁵
- Adoption of naloxone co-prescribing is low and inconsistent across states⁶

Recommend FDA Consider Opioid Label Updates and Regulatory Measures to Accelerate Naloxone Adoption to Mitigate Opioid Risks

1. Seth p CDC MMWR 2018;67:349–358 **2.** Jones CM. Drug Alcohol Depend. Sep 2013
3. Mattson CL CDC: MMWR Aug 2018 **4.** CDC Guideline for Prescribing Opioids for Chronic Pain **5.** See Joint Sponsor Briefing Note **6.** IQVIA Data

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Analysis of Unique Patients Filling Higher Risk Prescriptions

Analyzed IQVIA Patient Claims Data for Two Years to Sep 2018

- Opioid prescription numbers are higher than patient numbers because, on average, each patient fills 3.4 opioid prescriptions annually¹
- 97.3 million unique patients filled at least one opioid prescription
- 13.5 million unique patients had an opioid daily dose >50MME (Morphine Milligram Equivalents)
- 19.2 million unique patients had concurrent use of benzodiazepine/any opioid dose (4.7 million where opioid >50 MME)
- 1.6 million unique patients had naloxone/buprenorphine or buprenorphine prescription

34.2 Million (35%) Unique Patients Filled at Least One Prescription in the 2 year period that Met CDC Higher Overdose Risk² Criteria

1. CDC Drug Surveillance Report 2018. 2. CDC Guideline Recommendation 8: history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use.

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Nationally Narcan Nasal Spray is Narrowly Adopted

Analyzed IQVIA Patient Claims Data for Two Years to Sep 2018

- 0.8% patients with an opioid daily dose >50MME filled a Narcan Nasal Spray prescription
- 1.3% patients with concurrent use of benzodiazepine/any opioid dose filled a Narcan Nasal Spray prescription
- 5.7% patients with naloxone/buprenorphine or buprenorphine prescription filled a Narcan Nasal Spray prescription

1.3% of 34 Million Patients with a Higher Risk¹ Opioid Prescription Also Filled a Narcan Prescription in the 2 Year Period

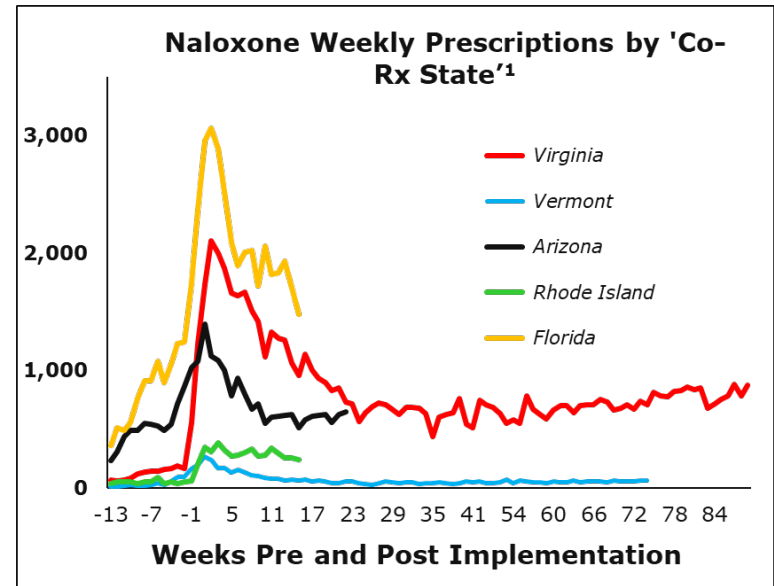
1. CDC Guideline Recommendation 8: history of overdose, history of substance use disorder, higher opioid dosages (=50 MME/day), or concurrent benzodiazepine use.

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Adoption is Higher in States Requiring Co-Rx

5 States Implemented Regulations Requiring Naloxone Prescribing with Higher Risk Opioids

- VA, VT, AZ, RI and FL ("Co-Rx States")
- WA and CA will implementing in 4Q18 and 1Q19
- Regulations are effective in accelerating adoption
- Initial spike post implementation
- 'Higher Risk Opioid' Criteria vary by State



Narcan Nasal Spray Adoption Was Up to 7 Times Higher In 'Co-Rx States'¹

- Up to 10.3% of patients with an opioid daily dose in excess of threshold filled a prescription¹
- Up to 8.1% of patients with concurrent use of benzodiazepine/any opioid dose filled a prescription¹
- Up to 8.3% patients with naloxone/buprenorphine or buprenorphine prescription filled a prescription¹

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Opioid Label Updates and Other FDA Regulatory Measures Could Expand Access

Estimated Additional 3M Patients Would Fill Narcan Nasal Spray

- Opioid label updates and other FDA regulatory measures could increase naloxone co-prescribing alongside the highest risk opioid prescriptions
- Estimates assuming;
 - FDA opioid label modification is based on CDC criteria
 - Utilizing the 5 'Co-Rx State' experience as a proxy
- Estimate that 3 million additional patients on higher risk opioid prescriptions would fill Narcan Nasal Spray prescription over 2 years

Narcan Nasal Spray Production Capacity

Significant Investment Initiated in mid-2018 to Expand Capacity

- 2018 production will be >3 million cartons (6 million devices) to meet demand
- Committed investments provide for doubling of capacity in 2019 and to up to 10 million units (20 million devices) in 2020
- On-going evaluation of additional investments to support demand increases

Managing Up-take Curve

- Developed a demand estimate assuming (i) FDA opioid label modification regulatory measure based on CDC criteria and (ii) using the 5 'Co-Rx State' experience as a proxy
- Expect to have adequate capacity to meet anticipated demand
- Plan an appropriate inventory build and to reserve units for Public Health consistent with past demand
- Recommend implementation lead-time to allow inventory build to meet expected spike in demand

Factors influencing access and adoption

Pharmacy Access

- State laws and regulations allow naloxone access without a personal prescription
- Pharmacy chains stock take-home naloxone and have in-store awareness initiatives

Financial Barrier

- Affordability to individuals, payors and public health
- Ensuring extensive health insurance with no or low out-of-pocket

Awareness of Opioid Risks and Naloxone

- Level of engagement by Payors, Pharmacists and Clinicians in identifying risk and raising awareness of opioid risks and naloxone

OTC Challenges

- Risk higher financial barrier for many without improvement in access or awareness

Narcan Nasal Spray Access & Affordability

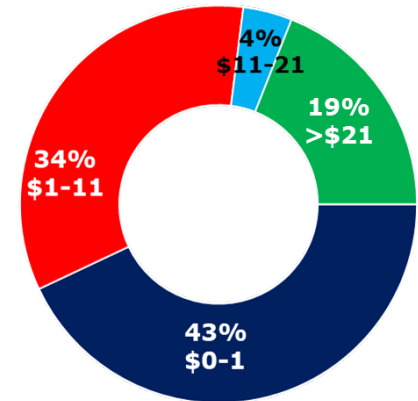
List Price & Discounted Public Interest Price

- Narcan Nasal Spray listed at \$125/carton (\$62.50/dose)
- No price increase since launch
- Discount of 40%+ is provided to all Public Health Purchasers, Medicaid, 340B, FSS to \leq \$75 per carton (\$37.50/dose)

Extensive Insurance Coverage at Affordable Co-pays¹

- 97% of private and public insured lives cover Narcan Nasal Spray
- Narcan Nasal Spray Co-pays: 77% <\$11
- Average co-pay of \$17.65 on dispensed prescriptions YE 1Q18

Patient Co-Pays on Dispensed
Narcan Nasal Spray YE 1Q18¹



Critical to continue focus on minimizing the financial barrier to access

1. IQVIA Formulary Impact Analyzer. Co-pays on dispensed prescriptions

Suggested FDA Regulatory Option & Cost

Modification to Opioid Labels (Indication Statement or Boxed Warning).

- Sample language: “[Because of the increased risk of opioid overdose], prescribe community use naloxone to (i) patients prescribed daily opioid dose of 50 morphine milligram equivalents (MME) or greater; or (ii) patients concurrently prescribed any opioid dose and benzodiazepines; or (iii) patients with a substance use disorder.”
- Amend the Communication Plan via the Medication Guide
- Incorporate into Opioid REMS Training Materials (Blueprint Has Been Updated)

Consider an Element To Assure Safe Use (ETASU) to the Opioid REMS if Label Amendment and Communication Plan are Ineffective in Expanding Access

Based on 3 Million Demand Estimate and Narcan Nasal Spray Cost, estimated cost of \$300M over 2 Years (c. 2.5% annual spend on opioids)

 **NARCAN**[®] (naloxone HCl)
NASAL SPRAY 4mg

protected by **emergent**
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FDA Advisory Committee

December 17 & 18 2018

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