© Copyright 2012 Oregon State University. All Rights Reserved

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Class Review: Opioid Reversal Agents

Date of Review: March 2016

Purpose for Class Review:
Agents for opioid reversal (i.e., opioid overdose) have not been formally reviewed by the Pharmacy & Therapeutics (P&T) Committee. Two new naloxone products, one intramuscular auto-injector formulation and one intranasal formulation, were recently approved by the United States (U.S.) Food and Drug Administration (FDA) which may offer convenient formulations for first responders and lay bystanders who witness an opioid overdose. In addition, more naloxone outreach programs have been developed as the opioid epidemic in the U.S. has grown. Organizations and government agencies have also provided guidance and recommendations for increased access to naloxone in the community.

Research Questions:
1. What are the differences in effectiveness of naloxone formulations or products when administered in the community by lay bystanders or first responders?
2. What are the differences in harms to opioid overdose victims or administering bystanders (i.e., seizures, agitation, needle sticks) of different naloxone formulations or products administered in the community?

Conclusions:
- There is low quality evidence that suggests no differences in *effectiveness* or *harms* between naloxone injectable formulations when given intramuscularly (0.4-2 mg) versus intranasally (2-4 mg) to reverse opioid overdose; however, more concentrated formulations (2 mg/1 mL) of injectable naloxone appear to be more effective than less concentrated formulations (2 mg/5 mL) when administered intranasally.[1–5]
- Naloxone HCl for injection has been available for over 40 years to reverse the effects of opioids in the medical setting. However, two new formulations, Evzio® auto-injector and Narcan® nasal spray may offer convenient alternatives to standard kits of naloxone HCl injectable solution (for intramuscular or intranasal use) for lay bystanders who witness an opioid overdose.[4,5] Both formulations were approved based on bioequivalence studies (similarities in pharmacokinetic parameters) with the reference drug naloxone HCl for injection.[4,5] There is insufficient evidence that directly compares the new formulations to each other or to standard naloxone kits.
- Increased access to naloxone for opioid users at high risk for opioid overdose is recommended by local and national organizations due to low quality evidence that increased naloxone availability in the community reduces rates of opioid overdose deaths.[6–9]

Recommendations:
- Limit the quantity of naloxone to 2 units every 12 months. OHP clients who require naloxone more frequently will be targeted by OHP for case management.
- Create a new PDL class for Opioid Reversal Agents and make Narcan® nasal spray preferred with open access.

Author: Andrew Gibler, PharmD Date: March 2016

Background:
Opiates and their synthetic analogs, collectively referred to as opioids, are a group of compounds that bind to opioid receptors located throughout the body.[8] Endogenous opiates activate μ, κ and δ-opioid receptors to produce analgesia but μ-opioid receptors in the brain stem are also used to modulate respiration in response to hypoxia and hypercapnia.[7] Thus, administered opioids can be potent respiratory depressants, which can result in hypoxemia leading to impaired consciousness or brain injury.[7] Cardiac arrest secondary to respiratory arrest is a late complication of opioid overdose.[7]

Opioid overdose is a leading cause of preventable death in the U.S.[8] Among people aged 25 to 64 years, overdose deaths from illicit drugs, which includes heroin and prescription opioid analgesics, now exceed traffic fatalities and are the leading cause of accidental deaths.[8] In 2013, there were more than 24,000 overdose deaths in the U.S. from prescription and illicit opioid drug use, a 3-fold increase since 1999.[8] The rise in opioid-related overdose deaths observed is associated with an increase in the prescribing of opioids for chronic pain.[7] On the contrary, a decrease in opioid overdoses may be associated with decreased prescribing of opioids in high risk populations.[10] In Oregon, the rate of opioid overdoses declined 38% between 2006 and 2013 (from 6.6 to 4.5 per 100,000 residents).[10] Oregon's rate of death from methadone decreased 58% in the same time period.[10] Key initiatives in Oregon that likely mitigated the adverse trend seen nationally included:

- Establishment of a PDMP to track prescriptions of controlled substances;
- Designation of methadone as a non-preferred drug under the OHP;
- Education and access of lay persons to provide naloxone to persons suspected of overdose; and
- Continuing education requirements for physicians and allied health care professionals about safe and effective pain care.[10]

People who take prescribed opioids are at lower risk for overdose than people who abuse opioids illicitly; yet, because of the vast volume of prescription opioid users, these patients make up a significant proportion of all overdoses.[7] The greatest risk factors associated with opioid overdose are injection or non-medical opioid use and reduced opioid tolerance, typically seen when opioid use is restarted after a period of abstinence (frequently occurs after release from incarceration or discharge from a detoxification program).[7] Patients at risk for prescription opioid overdose include those with higher prescribed doses.[7] For example, risk for overdose is significantly higher with prescribed daily doses of 100 mg morphine equivalents or more.[7] Other risks for prescription opioid overdose include polypharmacy (especially with benzodiazepines or other sedatives/hypnotics), mental health disorders, lower socioeconomic status, male gender, and older age.[7] Risk factors for opioid overdose are summarized in Table 1.

Table 1. Risk Factors for Opioid Overdose.[7–9]

• Opioid dependence and reduced tolerance (following detoxification, release from incarceration, cessation of treatment)
• History of opioid overdose
• Suspected history of substance abuse (including alcohol) or non-medical opioid use
• Use of high doses of prescription opioids (≥100 mg daily morphine equivalents)
• Use of opioids in combination with other sedating substances (e.g., benzodiazepines)
• Significant concurrent medical conditions (HIV, lung disease, liver disease, depression)
• Medicaid enrollees (6-times higher risk for opioid overdose death than people not enrolled in Medicaid)

Opioid overdose can be managed with basic life support resuscitation or timely administration of naloxone, an effective opioid antagonist that has been used to manage overdoses for over 40 years.[7] Naloxone is a competitive antagonist with high affinity for μ-opioid receptors.[6] Its safety is due to its specificity; its only

action is to rapidly displace most other opioids from opioid receptors and reverse opioid-mediated effects, which include respiratory depression, central nervous system depression and hypotension.[6] Naloxone has long been effective in the community if administered intravenously (IV), intramuscularly (IM), subcutaneously (SC) or intranasally (IN).[8] Until recently, naloxone kits for community distribution had to be assembled, which often include 1-2 vials or syringes of naloxone, needles for IM injection or an atomization device for IN administration. Recently, the FDA approved an auto-injector device (Evzio®) that delivers 0.4 mg/0.4 mL of naloxone for intramuscular or subcutaneous injection and an intranasal device (Narcan®) that delivers 4 mg/0.1 mL of naloxone into one nare.[4,5] Both formulations were approved based on bioequivalence studies with naloxone HCl for injection.[4,5]

Most opioid overdoses occur in private homes and are witnessed by friends, family or first responders.[7] Most bystanders do not call EMS when they witness an overdose because of perceived negative consequences if the overdose is reported.[3] Increased access to naloxone in the community could significantly reduce opioid overdose deaths;[7] but there is no evidence to suggest increased access to naloxone is associated with more illicit use of opioids. Expanding the availability of naloxone to first responders is also a key component of the overall strategy to reduce opioid overdose deaths.[8] Naloxone outreach programs are emerging among first responder organizations, law enforcement agencies, and public health needle exchange programs.[9] These outreach programs have distributed more than 150,000 doses of naloxone which directly contributed to a reduction in fatal opioid overdoses in the regions where these programs worked, with more than 26,000 cases of opioid overdoses reversed.[8] Naloxone administered by bystanders in the community has a successful resuscitation rate of 90% with a negligible rates of serious adverse events.[8]

Naloxone is only available by prescription in the U.S. but efforts underway may expand prescribing authority to pharmacists to improve access.[8,11] Naloxone can be prescribed to patients for use in an overdose emergency, and Oregon law allows naloxone to be prescribed to third party individuals who may witness an overdose.[9] A short training session (e.g., 10-20 minutes) in recognizing the signs of opioid overdose and the use of naloxone is adequate for safe use of naloxone in the community.[8] In Oregon, legal protections from civil liability are in place for those who administer naloxone after completion of adequate training.[11] Proper training is also essential because evidence suggests trained bystanders are more likely to use naloxone to reverse opioid overdose.[3]

Table 2 lists the currently available FDA-approved naloxone products. Table 3 summarizes the randomized, controlled trials (RCTs) published that compares different formulations of naloxone. A summary of relevant drug information is available in **Appendix 1**, which includes pharmacokinetic characteristics of naloxone formulations, as well as prescribing highlights for the Evzio® auto-injector product and the Narcan® intranasal product.

Table 2. Drug Products for Opioid Reversal.

Drug Name	Manufacturer	Strength	Usual Dose* and Route
Evzio® (naloxone)	Kaleo	0.4 mg/0.4 mL auto-injector	0.4 mg injection (IM or SC)
Naloxone HCl	Various	0.4 mg/mL 1- and 10-mL vials 2 mg/2 mL Luer lock syringe 1 mg/mL 2-mL vial	0.4 mg injection (IM, IV, IO, SC) (2 mg/2 mL syringe *may be used IN with a mucosal atomization device*)
Narcan® (naloxone)	Adapt Pharma	4 mg/0.1 mL	4 mg IN

Abbreviations: IM = intramuscular; IN = intranasal; IO = intraosseous; IV = intravenous; SC = subcutaneous

*The naloxone dose needed to achieve reversal of opioid overdose depends on the potency of opioid consumed, dose of opioid, other concurrently administered drugs (particularly sedatives) and many other factors. Naloxone dose should be titrated until clinical reversal is apparent.

Table 3. Summary of Comparative Trials.

Study	Comparison	Population	Primary Outcome	Results
Kelly, et al.[1] P, OL, RCT Setting: EMS, community	1. IN: naloxone 1 mg in each nare (total 2 mg/**5** mL) (n=84) 2. IM: naloxone 2 mg/5 mL IM (n=71)	Persons suspected of opioid overdose	Mean time to return of spontaneous respirations (RR >10 bpm)	• Mean time to return of spontaneous respirations IN: 8 min (95% CI, 7 to 8 min) IM: 6 min (95% CI, 5 to 7 min) Mean Difference 2 minutes (p=0.006) • % patients who required >1 dose of naloxone IN: 26% IM: 13% Mean Difference 13% (OR 2.4; 95% CI, 1.0 to 5.7; p=NS) • % patients with minor adverse effects IN: 12% IM: 21% Mean Difference 9% (p=NS)
Kerr, et al.[2] P, OL, RCT Setting: EMS, community	1. IN: naloxone 1 mg in each nare (total 2 mg/**1** mL) (n=83) 2. IM: naloxone 2 mg/5 mL IM (n=89)	Persons suspected of opioid overdose	% patients with effective and spontaneous respirations (RR ≥10 bpm) and/or GCS score ≥13 within 10 min	• % patients with successful reversal within 10 min IN: 72.3% IM: 77.5% Mean Difference -5.2% (95% CI, -18.2 to 7.7%; p=NS) • Mean response time IN: 8.0 min IM: 7.9 min Mean Difference 0.1 min (95% CI, -1.3 to 1.5 min; p=NS) • % patients who required >1 dose of naloxone IN: 18.1% IM: 4.5% Mean Difference 13.6% (95% CI, 4.2 to 22.9%; p=0.01) • % patients with minor adverse effects IN: 19.3% IM: 19.1% Mean Difference 0.2% (95% CI, -11.6 to 11.9%; p=NS)

Abbreviations: bpm = breaths per minute; CI = confidence interval; EMS = emergency medical services; GCS = Glasgow Coma Scale; IM = intramuscular; IN = intranasal; OL = open labeled; P = prospective; RCT = randomized, controlled trial; RR = respiratory rate

Note: Intranasal formulations in both studies were administered by LMA MAD mucosal atomization device (Teleflex, Inc., Research Triangle Park, NC).

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits

used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
None identified.

Guidelines:
Veterans Affairs (VA)
The VA Overdose Education and Naloxone Distribution (OEND) program is a harm reduction and risk mitigation initiative that aims to decrease opioid-related overdose deaths among VA patients.[6] The OEND program is involved in opioid overdose prevention, recognition and rescue response.[6] The program also issues naloxone kits (see Table 4) or the naloxone autoinjector device.[6] The OEND program prepared the following recommendations to provide standardized guidance on dispensing of these drug products:[6]

- A prescription is required for naloxone products.
- Naloxone should be discussed with patients and/or family or caregivers as an available option to mitigate risk.
- Naloxone should be offered to Veterans at increased risk for opioid overdose (i.e., opioid use disorder; prescription opioid misuse; or injection opioid use) or if there is an indication for naloxone based on clinical judgement.
- An IM or IN naloxone kit should be offered, rather than an autoinjector, except for those who are unable to demonstrate timely assembly and administration of the IM and IN naloxone kit.

Table 4. Naloxone Kit Contents.[6]

Intramuscular Naloxone Kit	**Intranasal Naloxone Kit**
(2) naloxone 0.4 mg/mL (1 mL) vials	(2) naloxone 1 mg/mL (2 mL) prefilled needleless syringe
(2) syringe, 3 mL with 25G 1-inch needle	(2) mucosal atomizer device
(2) alcohol pads	(1) face shield CPR barrier
(1) face shield CPR barrier	(1) pair of gloves
(1) pair of gloves	(1) overdose rescue instructions
(1) overdose rescue instructions	(1) opioid safety brochure
(1) opioid safety brochure	

World Health Organization (WHO)
The WHO issued guidelines on community management of opioid overdose in 2014.[7] Development of the guidelines began with the identification of key issues for which advice was needed. The WHO Steering Group and Guideline Development Group were established and clinical questions were formulated using the PICO format (population, intervention, comparator, outcomes) and systematic reviews were conducted for each PICO question. Evidence of values and

preferences, cost-effectiveness, feasibility and resource use was presented along with evidence of benefits and harms. Evidence-based recommendations for the availability of naloxone for people likely to witness an opioid overdose were formulated, along with advice on the resuscitation and post-resuscitation care of opioid overdose in the community.[7] The WHO recommendations that specifically pertain to naloxone are summarized in Table 5.

No studies identified by systematic review met the criteria for low risk of bias, but there were 20 studies that reported some overdose data for the provision of 'take-home' naloxone kits to people likely to witness an opioid overdose.[7] Data from case series estimate the mortality rate in opioid overdoses witnessed by people who have access to naloxone is 1.0% (95% CI, 0.83 to 1.21%).[7] In contrast, the mortality rate of opioid overdoses in communities where naloxone is not available has been estimated at 2-4%.[7] Acute opioid withdraw following administration of naloxone has been estimated to occur at a rate of 7.6% (95% CI, 4.9 to 10.2%) with seizures being reported in 0.45% of overdose reversals. [7] About 20% of naloxone doses distributed in observational studies are reported to be used.[7]

Only 2 studies fulfilled eligibility criteria that might address appropriate formulation and dosage of naloxone for initial management of opioid overdose.[7] Both were field-based RCTs that compared use of IN versus IM naloxone (initial 2 mg dose) by paramedics in people suspected of opioid overdose.[7] Meta-analysis of the 2 trials found no difference in effectiveness between administering IN naloxone versus IM naloxone.[7] Differences in rates of overdose complications (RR 0.36; 95% CI, 0.01 to 8.65), overdose morbidity (RR 0.85; 95% CI, 0.71 to 1.03), opioid withdrawal reaction to naloxone (RR 0.42; 95% CI, 0.10 to 1.65) or time to opioid reversal (mean difference (MD) 1.05 higher [95% CI, 0.81 lower to 2.91 higher]) also did not differ.[7] There were no deaths in either study.[7] Ease of administration was not evaluated. There were no studies that compared different initial doses or dosing regimens of naloxone (e.g., titration vs. single dose).[7]

Published surveys have shown a high degree of preparedness by non-medically trained persons to administer naloxone to family members, friends and strangers who have overdosed, with a preference for the IN formulation.[7] Initial parenteral (IV/IM/SC) doses of 0.4 mg to 2 mg are generally effective and occasionally 2 or more doses may be necessary.[7] In most cases, 0.4 to 0.8 mg is an effective initial dose for IM injection and higher initial doses increase the possibility of acute opioid withdrawal and seizures.[7] Intranasal administration generally requires a higher dose since the capacity of the nasal mucosa to absorb liquid is limited.[7]

Table 5. WHO Summary Recommendations.

Summary Recommendations	Strength of Recommendation*	Quality of Evidence
People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration.	Strong	Very low
Naloxone is effective when delivered by IV, IM, SC and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting and local context.	Conditional	Very low

* 'Strong': Guideline Development Group was confident that the evidence of effect, combined with certainty about the values, preferences, benefits and feasibility, make the recommendation one that should be applied in most circumstances and settings.
'Conditional': There is less certainty about the evidence of effect and values, preferences, benefits and feasibility around the recommendation. There may be circumstances or settings in which the recommendation does not apply.

References:

1. Kelly A, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust*. 2005;182:24-27.

2. Kerr D, Kelly A, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction*. 2009;104:2067-2074. doi:10.1111/j.1360-0443.2009.02724.x.

3. Clark A, Wilder C, Winstanley E. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med*. 2014;8:153-163.

4. Evzio (naloxone auto-injector) [Prescribing Information]. Richmond, VA: Kaleo; April 2014.

5. Narcan (naloxone nasal spray) [Prescribing Information]. Radnor, PA: Adapt Pharma, November 2015.

6. Recommendations for Issuing Naloxone Kits and Naloxone Autoinjectors for the VA Overdose Education and Naloxone Distribution (OEND) Program. VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives in collaboration with the VA OEND National Support and Development Work Group; June 2015. Available at http://www.pbm.va.gov/PBM/clinicalguidance/clinicalrecommendations/Naloxone_Kits_and_Autoinjector_Recommendations_for_Use_June_2015.pdf. Accessed 3 February 2016.

7. Community Management of Opioid Overdose. World Health Organization; 2014. Available at http://apps.who.int/iris/bitstream/10665/137462/1/9789241548816_eng.pdf?ua=1&ua=1. Accessed 14 January 2016.

8. Best Practices in Naloxone Treatment Programs for Opioid Overdose. Policy Report, July 2015. Oregon Health & Science University Center for Evidence-based Policy; Medicaid Evidence-based Decisions Project.

9. Reducing Opioid Overdose, Misuse and Dependency: A Guide for CCOs. Oregon Health Authority; October 2015. Available at http://www.oregon.gov/oha/healthplan/ContractorWorkgroupsMeetingMaterials/Reducing%20Opioid%20Overdose_A%20Guide%20for%20CCOs.pdf. Accessed 3 February 2016.

10. Centers for Disease Control and Prevention. State Successes of Prescription drug overdose data. Available at http://www.cdc.gov/drugoverdose/policy/successes.html. Accessed 18 February 2016.

11. ORS 689.681. Opiate Overdose.

Author: Andrew Gibler, PharmD

Date: March 2016

Appendix 1: Specific Drug Information[4,5]

Mean Pharmacokinetic Parameters (Relative Standard Deviation %) of Naloxone Nasal Spray and Intramuscular Injection of Naloxone to Healthy Subjects*[5]

Parameter	**4 mg** 1 Nasal Spray in 1 Nostril	**8 mg** 1 Nasal Spray in Each Nostril	**0.4 mg** Intramuscular Injection
T_{max} (hours)^	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
C_{max} (ng/mL)	4.83 (43.1)	9.70 (36.0)	0.88 (30.5)
AUC (hour*ng/mL)	7.87 (37.4)	15.3 (23.0)	1.72 (22.9)
$T_{1/2}$ (hours)	2.08 (29.5)	2.10 (32.4)	1.24 (25.9)
Dose Normalized Relative Bioavailability vs. Intramuscular Injection (%)	46.7 (31.4)	43.9 (23.8)	100

*healthy subjects were instructed not to breathe through the nose during administration of the nasal spray and remain fully supine for approximately 1 hour post-dose.

^ T_{max} reported as a median (minimum, maximum)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EVZIO safely and effectively. See full prescribing information for EVZIO.

EVZIO (naloxone hydrochloride injection) Auto-Injector for intramuscular or subcutaneous use
Initial U.S. Approval: 1971

----------INDICATIONS AND USAGE----------

EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. (1)
EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present. (1)
EVZIO is not a substitute for emergency medical care. (1)

----------DOSAGE AND ADMINISTRATION----------

- EVZIO is for intramuscular or subcutaneous use only. (2.1)
- Seek emergency medical care immediately after use. (2.1)
- Administer EVZIO to adult or pediatric patients into the anterolateral aspect of the thigh, through clothing if necessary. (2.2)
- Additional doses may be administered every 2 to 3 minutes until emergency medical assistance arrives. (2.2)
- In pediatric patients under the age of one, the caregiver should pinch the thigh muscle while administering the dose. (2.2)
- **If the electronic voice instruction system does not operate properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions on the flat surface of its label. (2.1)**

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 0.4 mg/0.4 mL naloxone hydrochloride solution in a pre-filled auto-injector. (3)

----------CONTRAINDICATIONS----------

Patients known to be hypersensitive to naloxone hydrochloride (4)

----------WARNINGS AND PRECAUTIONS----------

- Due to the duration of action, keep the patient under continued surveillance and repeated doses of naloxone should be administered, as necessary, while awaiting emergency medical assistance. (5.1)
- Other supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance. (5.1)
- Reversal of respiratory depression by partial agonists or mixed agonists/antagonists such as buprenorphine and pentazocine, may be incomplete. (5.2)
- Use in patients who are opioid dependent may precipitate acute abstinence syndrome. (5.3)
- Patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects should be monitored in an appropriate healthcare setting (5.3)
- In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. (5 3)

----------ADVERSE REACTIONS----------

The following adverse reactions have been identified during use of naloxone hydrochloride in the post-operative setting: Hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation. (6)

Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated signs and symptoms of opioid withdrawal including: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal signs and symptoms also included: convulsions, excessive crying, hyperactive reflexes. (6)

To report SUSPECTED ADVERSE REACTIONS, contact kaleo, Inc. at 1-855-773-8946 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 4/2014

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NARCAN NASAL SPRAY safely and effectively. See full prescribing information for NARCAN® NASAL SPRAY.

NARCAN® (naloxone hydrochloride) nasal spray
Initial U.S. Approval: 1971

----------INDICATIONS AND USAGE----------

NARCAN Nasal Spray is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. (1)

NARCAN Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present. (1)

NARCAN Nasal Spray is not a substitute for emergency medical care. (1)

----------DOSAGE AND ADMINISTRATION----------

- NARCAN Nasal Spray is for intranasal use only. (2.1)
- Seek emergency medical care immediately after use. (2.1)
- Administer a single spray of NARCAN Nasal Spray to adults or pediatric patients intranasally into one nostril. (2.2)
- Administer additional doses of NARCAN Nasal Spray, using a new nasal spray with each dose, if the patient does not respond or responds and then relapses into respiratory depression, additional doses of NARCAN Nasal Spray may be given every 2 to 3 minutes until emergency medical assistance arrives. (2.2)
- Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Nasal spray: 4 mg of naloxone hydrochloride in 0.1 mL (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to naloxone hydrochloride (4)

----------WARNINGS AND PRECAUTIONS----------

- Risk of Recurrent Respiratory and CNS Depression: Due to the duration of action of naloxone relative to the opioid, keep patient under continued surveillance and administer repeat doses of naloxone using a new nasal spray with each dose, as necessary, while awaiting emergency medical assistance. (5.1)
- Risk of Limited Efficacy with Partial Agonists or Mixed Agonists/Antagonists: Reversal of respiratory depression caused by partial agonists or mixed agonists/antagonists, such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses may be required. (5.2)
- Precipitation of Severe Opioid Withdrawal: Use in patients who are opioid dependent may precipitate opioid withdrawal. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. Monitor for the development of opioid withdrawal. (5.3)
- Risk of Cardiovascular (CV) Effects: Abrupt postoperative reversal of opioid depression may result in adverse CV effects. These events have primarily occurred in patients who had pre-existing CV disorders or received other drugs that may have similar adverse CV effects. Monitor these patients closely in an appropriate healthcare setting after use of naloxone hydrochloride. (5.3)

----------ADVERSE REACTIONS----------

The following adverse reactions were observed in a NARCAN Nasal Spray clinical study: increased blood pressure, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, and nasal inflammation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Adapt Pharma, Inc. at 1-844-4NARCAN (1-844-462-7226) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2015

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1946 to February Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 12, 2016

1 exp Naloxone/ 22984
2 exp Drug Overdose/ 8315
3 1 and 2 318
4 limit 3 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) 45