

FDA Briefing Document

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

December 17 - 18, 2018

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought background information related to naloxone products intended for use in the community to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
*Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and
Drug Safety & Risk Management Advisory Committee*

December 17-18, 2018

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**FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

MEMORANDUM

DATE: November 19, 2018

FROM: Joshua Lloyd, MD
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TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: December 17-18, 2018, AADPAC/DSaRM meeting to discuss strategies to increase the availability of naloxone products intended for use in the community

The misuse and abuse of illicit and prescription opioids and the associated risks of addiction, overdose, and death are a public health crisis in the United States. Opioid overdose is characterized by life threatening respiratory and central nervous system depression that, if not immediately treated, may lead to significant morbidity and mortality. Naloxone is an opioid antagonist that, when administered quickly after an opioid overdose, can save lives. Many organizations and local municipalities across the US have developed programs for making naloxone available in the community, and these programs have traditionally relied on the off-label use of commercially-available naloxone solutions in pre-packaged kits using a commercially-available nasal atomizer device and syringe for administration by the intranasal route, and less frequently, using a needle and syringe for administration by the intramuscular route. Training is generally provided on how and when to use these kits.

Because of the challenges associated with evaluating novel products intended to treat opioid overdose, an immediately life-threatening condition, in clinical studies when known effective doses of naloxone are available, the Agency has established an approach for the development of naloxone products for use in the community. This approach involves relying on the Agency's prior findings of safety and effectiveness for Narcan (naloxone hydrochloride; NDA 16636) and by a demonstration of systemic exposures that are no less than the exposures achieved with the minimum approved dose of Narcan, 0.4 mg by intravenous, intramuscular, or subcutaneous route, in pharmacokinetic studies conducted in healthy volunteers. There have been two

previous public meetings to discuss the development of naloxone for use in the community, one in 2012 and one in 2015. In addition, FDA has utilized various expedited programs for serious conditions to facilitate the development, review, and approval of naloxone products intended for use in the community.

As a result of these efforts, two naloxone products intended for use in the community have been approved for use in adult and pediatric patients. Evzio (naloxone hydrochloride injection) was initially approved on April 3, 2014, and is a prefilled auto-injector for intramuscular and subcutaneous use that is currently available as a single 2-mg dose of naloxone hydrochloride per injection. Narcan (naloxone hydrochloride) nasal spray was initially approved on November 18, 2015, and is currently available as a single 4-mg dose of naloxone in a 0.1 ml spray. Both products are packaged with two devices in a carton, in the event repeat administration is required.

Additionally, a joint meeting of AADPAC and DSaRM was held on October 5, 2016, to discuss the appropriateness of the current minimum standard of approval for naloxone products intended for use in the community, use in pediatrics, as well as other aspects of naloxone clinical development programs.

For this current meeting, we are asking input and advice on strategies to increase the availability of naloxone products intended for use in the community. In particular, we are asking the committees to consider various options for increasing access to naloxone, including whether naloxone should be co-prescribed with all or some opioid prescriptions to reduce the risk of overdose death. Because of the potential, significant costs and burdens that may be associated with naloxone co-prescribing (e.g., economic costs to consumers and health systems, adjusting to manufacturing volume growth, drug shortages), the committees will also be asked to consider the potential burdens that may be associated with naloxone co-prescribing for all or some patients receiving prescription opioids. The committees will be asked to consider co-prescribing in relation to other strategies for increasing naloxone availability, and to advise the Agency on what strategies are known to be the most effective for getting naloxone into the community to prevent opioid overdose deaths.

The committees will be asked to discuss the most relevant strategies for increasing access to naloxone in the community, considering different populations, potential costs, barriers to implementation, and relative benefits of different approaches.

These are clearly difficult questions for which there are no easy answers. We are asking that you provide your expertise, your experience and your best insights to help us find a reasonable and responsible path forward. Your advice and recommendations will be essential in assisting us with addressing this complex and critical public health concern. We are grateful that you have agreed to join us for this important discussion and look forward to seeing you at the meeting.

Draft Points for Discussion

- Naloxone is currently made available to the community through overdose education and naloxone distribution (OEND) programs, prescribing programs in health care settings (e.g. pain clinics and opioid treatment programs), or “take-home” programs for higher risk populations. Discuss the comparative and collective effectiveness of these programs with regard to prevention of overdose and their ability to get naloxone where it is most needed in communities to save lives.
- Discuss potential costs, burdens and/or barriers that may be associated with naloxone co-prescribing for all or some patients prescribed opioids, as well for OEND programs and take-home programs.
- Because of the potential for significant costs associated with increasing naloxone availability, prioritization of strategies will likely be needed. Discuss whether:
 - (a) alternate methods of increasing naloxone availability should be prioritized over co-prescribing, and whether these alternate methods (e.g., community-based distribution programs, or “take-home” programs in high-risk populations) are preferable based on available data on effectiveness and costs of these alternate methods.
 - (b) co-prescribing should be limited to certain populations that may potentially benefit the most from having naloxone available (i.e., those at highest risk for overdose), and identify those populations, along with the evidence supporting this benefit.
- Discuss the magnitude of the overall public health benefit associated with naloxone co-prescribing versus other methods to increase naloxone availability in the community to ensure it is available in the situations where it is most needed.
- Discuss any potential unintended consequences that should be considered if naloxone is co-prescribed with some or all prescription opioids.
- Would labeling language for some or all prescription opioids that recommends co-prescription of naloxone be a useful method for expanding access to naloxone?
 - Will those at highest risk for overdose benefit from labeling that recommends co-prescription of naloxone with some or all prescription opioids?



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

MEMORANDUM

DATE: November 19, 2018

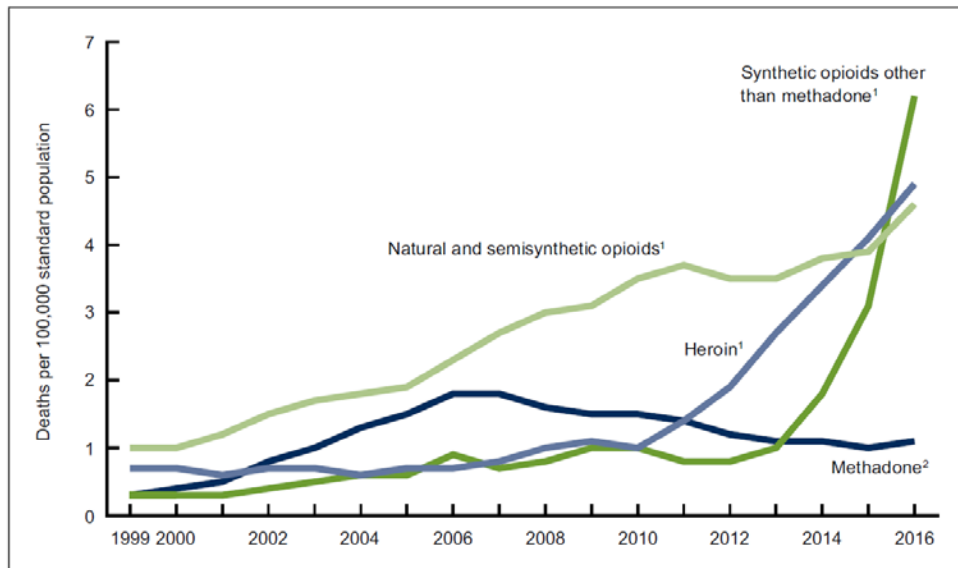
FROM: Timothy Jiang, MD, PhD
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Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: December 17-18, 2018, AADPAC/DSaRM meeting to discuss strategies to increase the availability of naloxone products intended for use in the community

1. Background

The United States is in the midst of a public health crisis related to the abuse of, misuse of, and addiction to opioid drugs.¹⁻⁵ This crisis has taken a staggering toll with an estimated 2 million Americans having a substance use disorder involving prescription pain relievers and 591,000 having a substance use disorder involving heroin.⁶ In recent years, there has been a marked increase in the number of opioid-related overdose deaths driven by heroin and synthetic opioids other than methadone, as shown in the figure below.⁷



¹Significant increasing trend from 1999 to 2016 with different rates of change over time, $p < 0.05$.

²Significant increasing trend from 1999 to 2006, then decreasing trend from 2006 to 2016, $p < 0.05$.

NOTES: Deaths are classified using the *International Classification of Diseases, Tenth Revision*. Drug-poisoning (overdose) deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes: heroin, T40.1; natural and semisynthetic opioids, T40.2; methadone, T40.3; and synthetic opioids other than methadone, T40.4. Deaths involving more than one opioid category (e.g., a death involving both methadone and a natural or semisynthetic opioid) are counted in both categories. The percentage of drug overdose deaths that identified the specific drugs involved varied by year, with ranges of 75%–79% from 1999 to 2013, and 81%–85% from 2014 to 2016. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db294_table.pdf#4. SOURCE: NCHS, National Vital Statistics System, Mortality.

In many cases, life-threatening respiratory depression due to opioids can be successfully reversed by timely administration of naloxone, a drug that blocks the effects of opioids. The utility of naloxone in saving lives is reflected in the endorsement of the Department of Health and Human Services, where “promoting use of overdose-reversing drugs” is one of the five priorities to combat the opioid crisis.⁸ The Commissioner of the FDA, Scott Gottlieb, MD, specifically noted that the Agency is focused on increasing the use and access to the potentially life-saving antidote naloxone.⁹

As noted in prior public meetings pertaining to naloxone products,^{10,11} FDA is committed to increasing the availability of naloxone products intended for use in the community. FDA has been facilitating the development and approval of new naloxone products for use in the community by non-medically-trained persons and is working to foster the development of naloxone products for over-the-counter use as a means to increase its availability in the community.^{12,13} The Agency could also consider additional actions including revision of the labeling for some or all opioid-containing drug products to inform prescribers about the existence of naloxone products, or to advise prescribers to consider or to recommend co-prescription of naloxone.

Ideally, all patients who are prescribed opioids would also have naloxone available for use in the event of an overdose of the patient or another member of the household accidentally exposed to the opioid. Unfortunately, healthcare resources are limited and the retail price of the approved naloxone products for community use can be high (as much as ~\$4000 for a package containing 2 units of one product). CDER’s Economic Analysis Group has conducted an analysis to assess the potential costs of naloxone co-prescribing, included elsewhere in this background package and has concluded that the cost of co-prescription can be substantial, depending on the assumptions made. However, lives saved by naloxone may also result in associated realized economic benefits that should be considered along with the potential costs.

When discussing whether naloxone co-prescribing should be targeted to all or some patients prescribed opioids, a couple of additional considerations are worth noting. While prescription opioids contribute to a substantial proportion of overall opioid-related morbidity, recent data suggest that a substantial and growing percentage of opioid-related deaths are associated with the use of illicit opioids. As a result, co-prescription of naloxone may not reach a large proportion of individuals at risk for an opioid overdose death. Additionally, in order for reversal of an opioid overdose to be successful, it must be administered soon enough to prevent irreversible anoxic injury to the brain. In some cases, this means the overdose would need to be witnessed for naloxone administration to be early enough to rescue the patient.

2. Naloxone Pharmacology and Pharmacokinetics

Naloxone is a small molecule antagonist that acts at the mu-opioid receptor. It was initially approved in the United States in 1971 with the tradename Narcan. Narcan, as originally approved, is an injectable naloxone product that can be delivered via the intravenous (IV), intramuscular (IM), or subcutaneous (SC) routes of administration and is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids. Narcan is also indicated for the diagnosis of suspected or known acute opioid overdosage. Earlier formulations of naloxone and its generic equivalents are not optimized for use by non-medical professionals although, as described in Section 3 below, some unapproved kits include these products for use in the community.

The currently approved labeling for Narcan (naloxone hydrochloride) injection is included in another section of this background document for reference.

3. Approved and Unapproved Indications and Uses for Naloxone Products Intended for Use in the Community

Two naloxone products intended for use in the community have been approved for use in adult and pediatric patients. Evzio (naloxone hydrochloride injection) was initially approved on April 3, 2014, and is a prefilled single-use auto-injector for intramuscular and subcutaneous use that is currently available as a 2-mg dose of naloxone hydrochloride per injection. Narcan (naloxone hydrochloride) nasal spray was initially approved on November 18, 2015, and is currently available as a single-use device with a 4-mg dose of naloxone in a 0.1 ml spray. Both products are packaged with two devices in a carton, in the event repeat administration is required.

The approved naloxone products intended for use in the community are indicated for:

- 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

Additionally, improvised naloxone products are being used in some community settings to reverse opioid overdose. One such product is supplied as a kit consisting of injectable 2 mg/2 ml naloxone in a prefilled syringe with a mucosal atomizer device to allow for intranasal delivery. Half of the volume (1 ml) is sprayed in one nostril and the remaining volume (1 ml) is sprayed into the other nostril. The injectable product that is being used in these kits is not approved for intranasal use. Other products are supplied as kits containing naloxone intended for subcutaneous or intramuscular injection.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)
Department of Epidemiology II**

**Epidemiology Review:
Data and published literature on the prescribing and distribution of naloxone**

Date:	November 5, 2018
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Deputy Director for Drug Utilization:	LCDR Grace P. Chai, PharmD Division of Epidemiology II
Associate Director for Public Health Initiatives:	Judy Staffa, PhD, RPh Office of Surveillance and Epidemiology (OSE)
Subject:	A synthesis of current data and published literature on the prescribing and distribution of naloxone to patient-populations, including those using opioid analgesics or medication assisted treatment (MAT) opioids, and other at-risk populations, with a focus on measures of distribution program effectiveness
Drug Name(s):	naloxone hydrochloride
Application Type/Number:	multiple
OSE RCM #:	2018-2286

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EXECUTIVE SUMMARY

On December 17th and 18th, 2018, the Food and Drug Administration (FDA) will hold a public meeting to discuss strategies to increase the availability of naloxone products intended for use in the community. As background for this meeting, the Division of Epidemiology (DEPI) undertook this review to provide the committee with information on methods of naloxone distribution, and data on reported naloxone use and opioid overdose reversals.

DEPI used proprietary drug utilization databases available to the FDA to estimate nationally estimated sales and dispensed prescriptions for naloxone products. Sales data for 2017 showed that ~83% of naloxone units (e.g., vials, auto-injectors, nasal sprays) were sold to non-retail settings of care, primarily to non-federal hospital and clinics, institutions which may also supply first responders and emergency medical services. An estimated 17% of sales were to retail and mail-order/specialty pharmacies, an increase from approximately 3% of total sales in 2013. Naloxone sales to all settings of care doubled from ~2.5 million units sold in 2013 to ~5.0 million units sold in 2017. The retail setting accounted for a small but growing proportion of total naloxone availability. The nationally estimated number of naloxone prescriptions dispensed from U.S. outpatient retail pharmacies more than doubled from 134,000 prescriptions dispensed in 2016 to 330,000 prescriptions dispensed in 2017. Over 70% of total naloxone prescriptions dispensed in 2017 were for the FDA approved nasal spray formulation of naloxone.

DEPI also conducted a comprehensive literature search to identify publications that described various types of naloxone distribution programs and included outcome measures suggestive of program effectiveness (e.g., opioid overdose reversals and mortality). The published studies on naloxone distribution programs were organized into three broad, and somewhat overlapping categories: 1) community-based programs outside of traditional health care settings, 2) prescribing programs in health care settings, and 3) “take-home” naloxone programs for populations at acute risk for overdose.

For the first group, data on community-based programs come from studies of overdose education and naloxone distribution (OEND) programs that use a diffuse network of organizations throughout a defined community for naloxone trainings, where naloxone is directly provided on-site. For the second group, data from prescribing programs come from programs housed in more traditional health care settings, where naloxone prescriptions can be provided to those also prescribed opioid analgesics and/or opioids for medication-assisted treatment (MAT), and where additional naloxone prescriptions can be provided as needed. For the third group, these studies focused on “take-home” naloxone programs designed for people who may be at acute risk for overdose (e.g., recently released from incarceration, presenting at needle exchange centers, discharged from the emergency department or hospital after an overdose event), where naloxone kits are distributed at a single point in time without planned follow-up assessments for further naloxone dispensation.

Despite some clear differences in distribution modalities, all three categories of studies suggest that providing naloxone to those who may or may not overtly express the need for it results in rescue attempts (i.e., the naloxone was administered, but may or may not

have resulted in an opioid reversal). Evidence suggests a utility in naloxone access for a range of potential at-risk populations, including patient populations and those engaged in community programs. Rescue attempts were observed in those who received the naloxone as well as in others proximal to the person who received the naloxone, such as friends, family, or acquaintances.

Community-based OEND programs have been operational across the U.S. since 1996, reporting thousands of rescue attempts from the naloxone they distributed. Some ecological studies suggest that communities with greater access to OEND programs have more opioid overdose reversals and lower mortality than communities with less access. Direct prescribing programs aimed at those using opioid analgesics or opioids for MAT, or those in treatment for substance use disorder, are generally designed as either targeted prescribing or “universal precaution” prescribing (i.e., prescribing to all patients regardless of perceived risk), and it appears that targeted prescribing may be more common in practice; data are limited with respect to “universal precaution” prescribing. Like community-based OEND and direct prescribing programs, “take-home” naloxone programs designed for those at acute risk for overdose also result in rescue attempts. Ecological data may support the utility of targeting these specific high-risk populations for “take-home” naloxone provisions, but further research is needed using more rigorous study designs.

Overall, data on naloxone availability and rescue attempts associated with naloxone distribution from any modality are very limited. Access to naloxone is possible through a variety of pathways, such as through “standing order” prescriptions or through donations from manufacturers, that make it difficult to track and enumerate as proprietary drug utilization databases are typically limited to data on sales and prescription transactions. In the literature, data on naloxone distribution come from small, descriptive surveys of mostly convenience samples with often short and inconsistent follow-up. It is unclear whether findings from these studies are representative of other similar programs, or programs in other geographic areas. Data on naloxone rescue attempts generally relied on self-report, without independent data verification, and because follow-up response rates are low, it was not clear how many kits were ultimately used or how many lives were saved. Therefore, data on actual naloxone use and opioid overdose reversals from community-based or “take-home” programs may be an underestimate. For studies on naloxone prescribing programs, it can be difficult to assess the impact of confounding by indication in relation to who ultimately uses the naloxone, as targeted prescribing, rather than “universal precaution” prescribing, appears to be more common. Publication bias resulting from the publication of data from only successful programs must also be considered.

The generalizability of these descriptive surveys is uncertain; however, in this analysis we viewed these data as similar to published case reports, capturing distribution and utilization of community-use naloxone, and helpful in informing further research on naloxone use. There is still a clear need for improved survey studies with a complete accounting of all naloxone distribution and administration. Also, randomized and/or prospective observational studies to better understand the relative effectiveness of various types of naloxone distribution programs, and ways to maximize the potential impact of those programs, are warranted. In the absence of data from more rigorous study designs,

studies using advanced modeling methods with “real world” data inputs may be helpful in generating hypotheses and informing future research efforts.

1 INTRODUCTION

1.1 BACKGROUND

On December 17th and 18th, 2018, the Food and Drug Administration (FDA) will hold a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The general function of an advisory committee meeting is to provide advice and recommendations to FDA on regulatory issues.

The purpose of this specific meeting is for the Agency to receive input and advice on strategies to increase the availability of naloxone products intended for use in the community. The committees will be asked to consider various options for increasing access to naloxone, weighing logistical, economic, and harm reduction aspects and whether naloxone should be co-prescribed with all or some opioid prescriptions to reduce the risk of overdose death. Because of the potential, significant costs, challenges, and burdens as well as unintended consequences that may be associated with naloxone co-prescribing (e.g., economic costs to consumers and health systems, adjusting to manufacturing volume growth, drug shortages, unintended public health consequences), the committees will also be asked to consider the potential burdens that may be associated with naloxone co-prescribing for all or some patients receiving prescription opioids.

The Division of Epidemiology (DEPI) undertook this review to provide the committee with a summary of information germane to the topic of the meeting, including data from proprietary drug utilization databases available to the Agency, and from the medical literature, specifically data on current naloxone use and methods of naloxone distribution, and data on the effectiveness of various naloxone distribution models vis-à-vis opioid overdose reversals and reducing opioid overdose mortality.

1.2 REGULATORY HISTORY

Naloxone hydrochloride (originally approved in 1971) 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. Naloxone is currently available in several strengths and formulations including injectable, auto-injector, and nasal spray (**See Table 1**). Naloxone competes for *mu* opioid receptors in the central nervous system, displacing agonist actions from opioids and reversing the effects of respiratory depression and sedation.

Table 1: Marketed naloxone products

Product	Strength	Formulation	NDA	Initial Approval date
Branded Products				
Adapt® Pharma. (Narcan® Nasal Spray)	4mg/0.1ml	Nasal spray	208411	11/18/2015
Kaleo® Pharma (EVZIO®)	0.4mg/0.4ml 2.0mg/0.4ml	Auto-injection	209862	04/03/2014 (D/C) 10/19/2016
Generic Products				
Hikma Pharmaceuticals USA Inc. (West-Ward Pharmaceuticals)	0.4mg/ml	Injection	070299	10/22/1985
Mylan®	0.4mg/ml	Injection	204997	03/06/2014
Hospira®	0.4mg/ml	Injection	070172	04/18/1986
Amphastar® (International Medication Systems)	0.4mg/ml 2mg/2ml	Injection Injection	070639 072076	01/17/1986 03/24/1988
Akorn	0.4mg/1ml 4.0mg/10ml	Injection Injection	208871 208872	2/28/2017 3/14/2017
Somerset Therapeutics LLC	0.4mg/ml	Injection	207633 207634	7/26/2017

Source: Drugs@FDA.com. Accessed 10/01/2018

2 REVIEW METHODS AND MATERIALS

2.1 DRUG UTILIZATION ANALYSES

Proprietary drug utilization databases available to the Agency were used to conduct these analyses; see **Appendix A** for detailed descriptions and limitations of the databases. In this review, a “naloxone unit” refers to all naloxone product formulations, including the auto-injector, nasal spray, and injectable formulations.

To determine the various settings of care where naloxone is distributed, the IQVIA, National Sales Perspectives™ (NSP) database was used to obtain nationally estimated number of naloxone units (e.g., auto-injector, nasal spray, vial) sold from manufacturers to all U.S. channels of distribution from January 2013 through December 2017. In this review, a unit refers to an entity for single administration of naloxone. A package may contain two units of naloxone for example two auto-injectors, or two nasal sprays. The sales distribution data do not reflect what is being sold to or administered to patients

directly; rather, these data provide a national estimate of units sold from the manufacturer into various channels of distribution. Of note, donations and some direct sales of naloxone are not captured in this data source.

The IQVIA, National Prescription Audit™ (NPA) database was used to obtain the nationally estimated number of prescriptions dispensed for naloxone from January 2013 through December 2017, annually. In addition, prescriber specialties generating prescriptions for naloxone from U.S. outpatient retail pharmacies were identified from this database.

The Symphony Health Solution, PHAST Prescription Monthly, database was used to obtain the nationally estimated number of prescriptions dispensed for naloxone and narcotic analgesics, grouped by U.S. state, from outpatient mail-order and retail pharmacies, in 2016 and 2017.

Data obtained from Sponsors regarding distribution of naloxone products were also included in this review. Permission was received from two sponsors (Adapt Pharma and Kaleo) to present data on the quantity of naloxone products distributed through donation pathways. These data provide insight into non-transaction related distribution of naloxone.

2.2 LITERATURE SEARCH

On October 15th, 2018, DEPI conducted a comprehensive literature search using the PubMed and Embase databases. DEPI employed a search strategy to identify publications where various types of naloxone distribution programs are described (e.g, community-based distribution programs, individual prescribing programs, “take-home” programs), and outcomes that could inform program effectiveness are measured (e.g., opioid overdose reversals, mortality).

First, the following search terms were used in PubMed and Embase, searching for human studies that were published between October 15th, 2008, and October 15th, 2018:

PubMed – search yielded 516 references

("naloxone"[MeSH Terms] OR "naloxone"[All Fields]) AND (("prescriptions"[MeSH Terms] OR "prescriptions"[All Fields] OR "prescription"[All Fields]) OR ("supply and distribution"[Subheading] OR ("supply"[All Fields] AND "distribution"[All Fields]) OR "supply and distribution"[All Fields] OR "distribution"[All Fields]) OR ("supply and distribution"[Subheading] OR ("supply"[All Fields] AND "distribution"[All Fields]) OR "supply and distribution"[All Fields] OR "supply"[All Fields]) OR take-home[All Fields]) AND ("2008/10/18"[PDat] : "2018/10/15"[PDat] AND "humans"[MeSH Terms])

Embase– search yielded 519 references

('naloxone'/exp OR naloxone) AND ('prescription'/exp OR prescription OR 'distribution'/exp OR distribution OR supply OR 'take home') AND 'human'/de AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND 'article'/it AND 'naloxone'/de

We reviewed the references captured through these searches, and we identified relevant studies that quantified naloxone use, opioid overdose reversals, or other outcomes (e.g., opioid overdose deaths, opioid-related emergency department visits), or evaluated models of naloxone distribution. Then, we reviewed several published systematic reviews (N=10)¹⁻¹⁰ on naloxone distribution programs to identify any additional studies not captured in the database searches. We did not include studies on naloxone use from first-responders (e.g., fire-fighters, police officers, or emergency medical service workers) because in these types of settings naloxone is generally not distributed prophylactically as is typical in all other distribution modalities.

In total, 50 studies were deemed specifically relevant to this advisory committee meeting with respect to current naloxone distribution models, and measures of their effectiveness. DEPI reviewed and summarized the results of these studies (**Section 3.5 and Appendix C**).

3 DATA SYNTHESIS

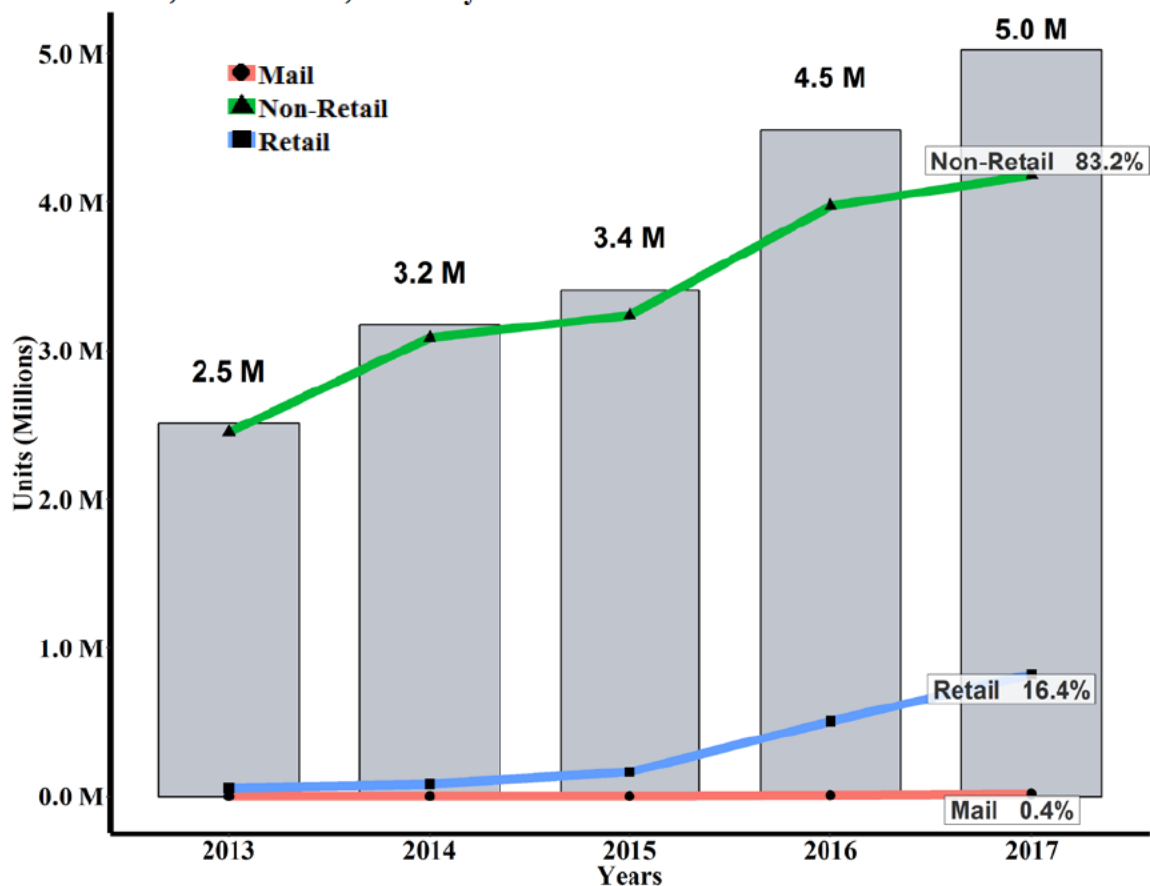
3.1 DRUG UTILIZATION RESULTS

3.1.1 Naloxone sales distribution data

Figure 1 below and Table 1 in Appendix B provide the nationally estimated number naloxone units (e.g., vial, spray, auto-injector) sold by manufacturers to major channels of distribution, from January 2013 through December 2017, annually. Naloxone sales gradually doubled from approximately 2.5 million units sold in 2013 to approximately 5 million units sold in 2017. Sales data for 2017 showed that approximately 83% of naloxone units were sold to non-retail settings and 17% to retail and mail-order/specialty pharmacies. The majority of sales (more than 50%) within the non-retail setting of care were to non-federal hospitals and clinics. Non-retail channels include the following sub-channels: non-federal hospitals, federal facilities, long-term care, HMOs, clinics, home health, and miscellaneous (including prisons and universities). Although small, the retail channel had the largest percentage increase over the examined time-period compared to non-retail channels.

Figure 1

Nationally estimated number of naloxone units (auto-injector, nasal spray and injection formulation) sold from manufacturers to various U.S. channels of distribution, 2013 – 2017, annually



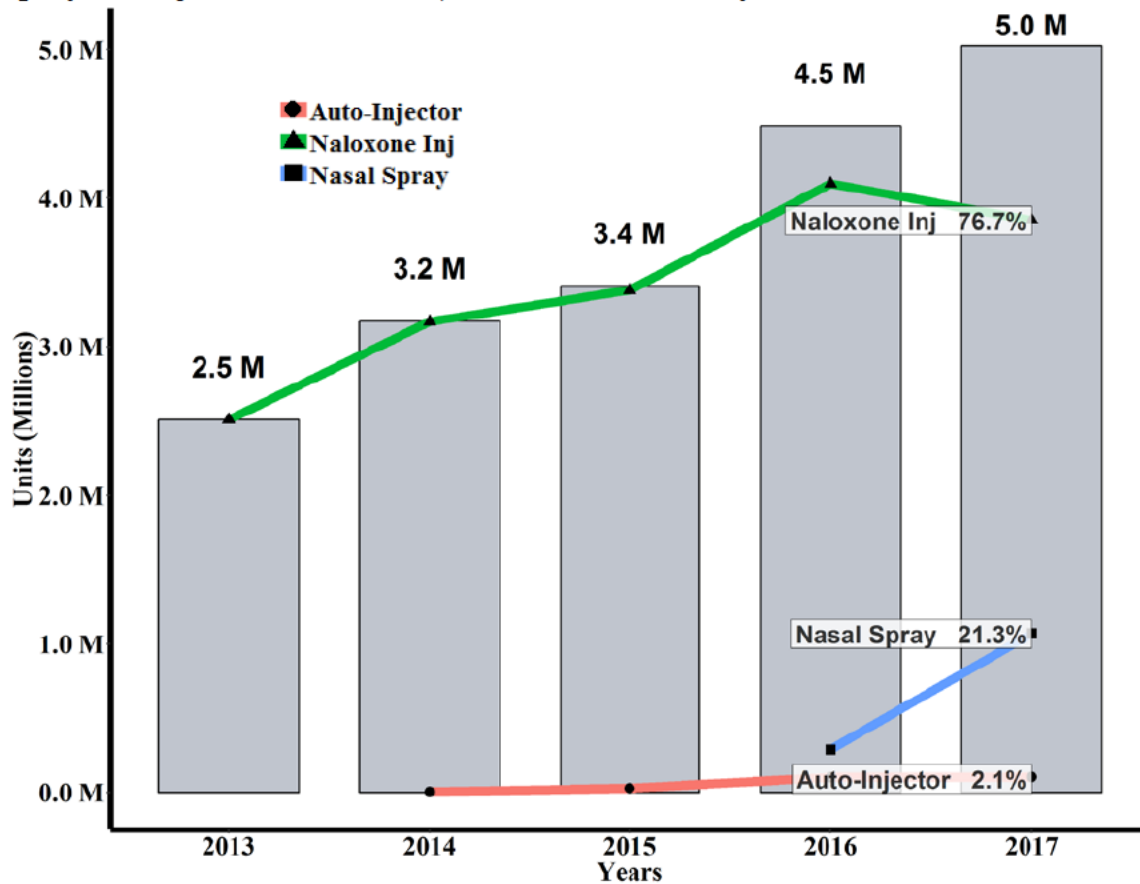
Source: IQVIA, National Sales Perspective(NSP). January 2013-December 2017. Data Extracted October 2018. File: 2018-1663 NSP naloxone. 9-12-2018.

Non-retail channels: non-federal hospitals, federal facilities, long-term care, HMOs, clinics, home health, and miscellaneous (including prisons and universities),

Figure 2 below and Table 2 in Appendix B provide the nationally estimated number of naloxone units stratified by formulation (auto-injector, nasal spray and injection formulation) sold by manufacturers from January 2013 through December 2017, annually. The majority of naloxone units sold over the examined time period were for injectable formulations. The majority of sales to the retail pharmacy setting were for the nasal formulation of naloxone which was approved for marketing in late 2015.

Figure 2

Nationally estimated number of naloxone units sold from manufacturers to various U.S. channels of distribution, stratified by product formulation (auto-injector, nasal spray and injection formulation), 2013 – 2017 annually

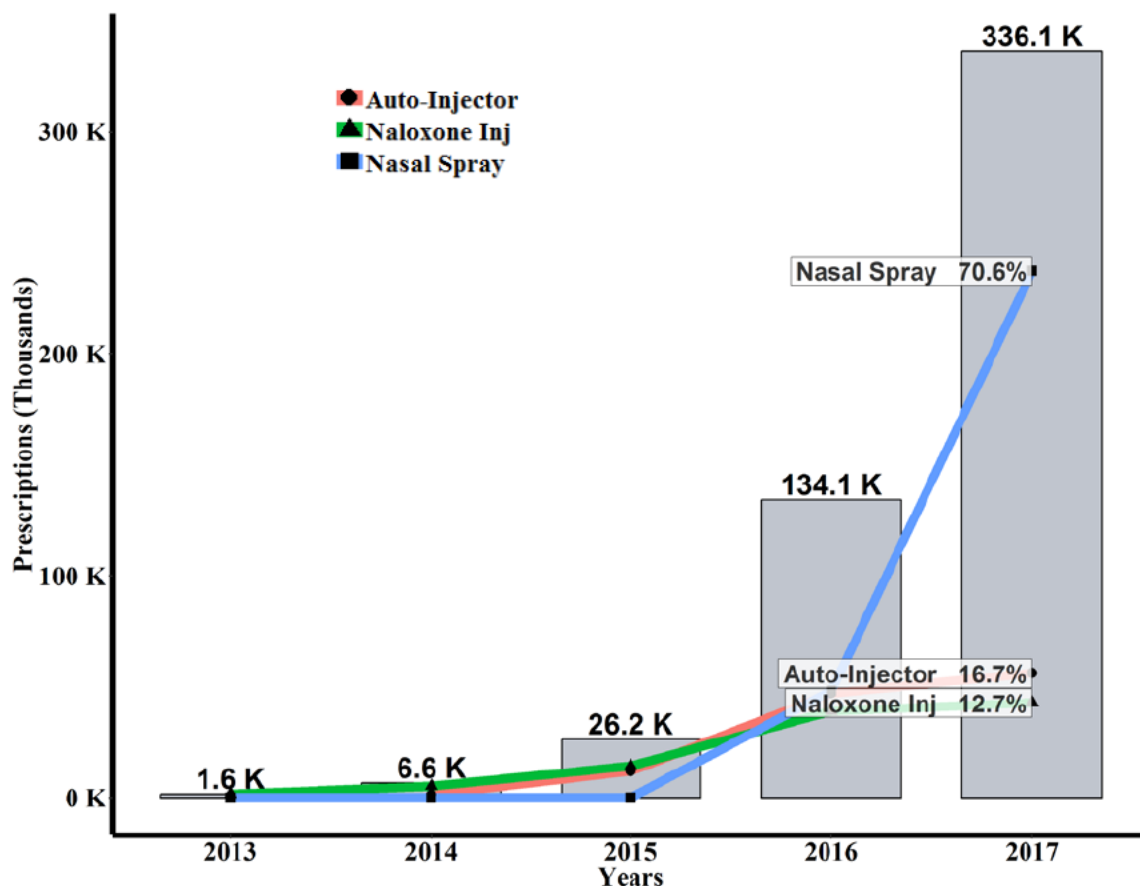


3.1.2 Dispensed prescription data

Figure 3 below and Table 2 in Appendix B provide the nationally estimated number of naloxone prescriptions dispensed from U.S. outpatient retail pharmacies, stratified by formulation (auto-injector, nasal spray and injection formulation), from January 2013 through December 2017, annually. The estimated number of naloxone prescriptions dispensed more than doubled from approximately 134,000 prescriptions dispensed in 2016 to more than 330,000 prescriptions dispensed in 2017. Over 70% of total naloxone prescriptions dispensed through U.S. retail pharmacies in 2017 were for nasal spray formulation of naloxone.

Figure 3

Nationally estimated number of naloxone prescriptions, stratified by product formulation (auto injector, nasal spray and injection), dispensed from U.S. outpatient retail pharmacies 2013 – 2017 annually.



Source: IQVIA, National Prescription Audit(NPA) January 2013,- December 2017. Data Extracted October 2018. File: 2018-1663 NPA naloxone. 9-26-2018.

Table 3 in Appendix B provides the nationally estimated number of prescriptions of naloxone dispensed from U.S. outpatient retail pharmacies, stratified by provider specialty in 2017. More than 50% of prescriptions dispensed were written by mid-level practitioners (nurse practitioners and physician assistants) and generalists (family practice, general practice, and internal medicine specialties). Less than 1% of naloxone prescriptions dispensed were written by addiction medicine specialties in 2017.

Of note, many states have implemented programs using “standing order” prescriptions. A “standing order” is a physician’s order that can be carried out by other health care workers or pharmacies when predetermined conditions have been met. Under this model, a doctor with prescriptive authority issues a written order that naloxone can be dispensed by designated people, such as pharmacists. Thus, someone can receive naloxone without

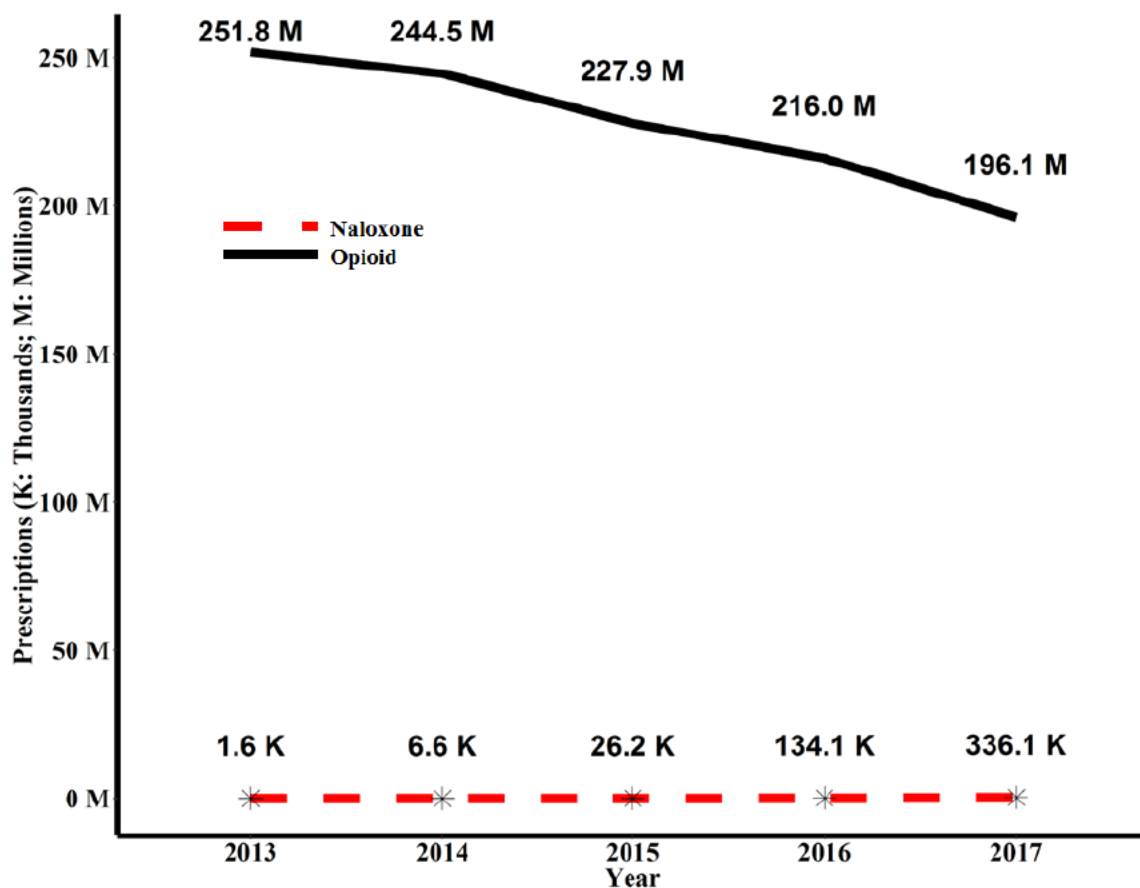
ever meeting the doctor who prescribed it. Some “standing orders” are written so that distribution is not limited to the individual at risk of overdose. In these cases, a potential bystander, such as a family member, could procure naloxone to administer in an emergency. Our prescriber specialty analysis includes prescribers who may have written “standing order” naloxone prescriptions, and therefore, these data may not accurately reflect from whom some patients procured the naloxone.

3.2 OPIOID ANALGESICS AND NALOXONE PRESCRIPTION DATA

Figure 4 below and Table 4 in Appendix B provide nationally estimated number of naloxone prescriptions and opioid analgesic prescriptions dispensed from U.S. outpatient retail pharmacies, 2013-2017. The amount of opioid analgesic prescriptions dispensed far surpasses the naloxone prescriptions dispensed from outpatient retail pharmacies by several orders of magnitude each year over the examined period. Of note, these naloxone prescription data are estimates of naloxone dispensed out of retail pharmacies, and they do not represent the total naloxone available to patients or the community.

Figure 4

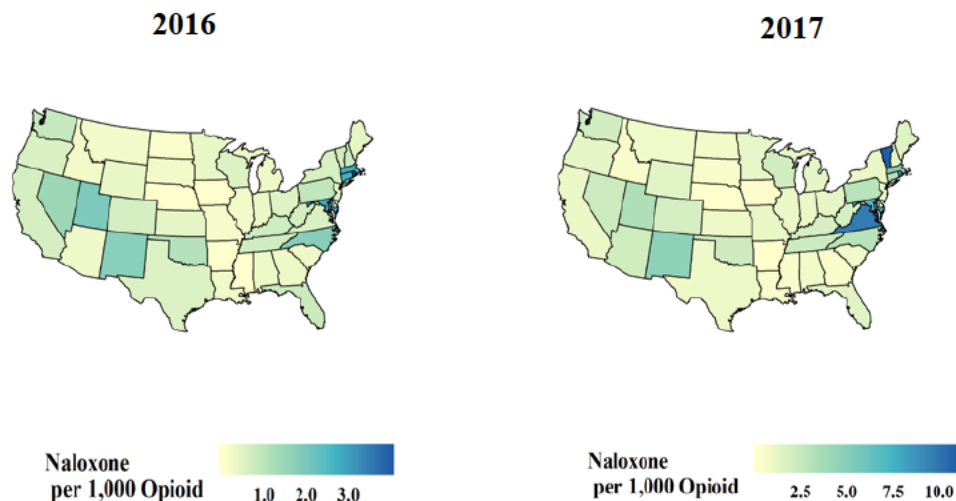
Nationally estimated number of naloxone prescriptions (all formulations, red line) and opioid analgesic prescriptions (black line) dispensed from U.S. outpatient retail pharmacies, 2012 – 2017 annually.



Source: IQVIA, National Prescription Audit (NPA), National Prescription Audit (NPA). January 2013–December 2017. Data Extracted October 2018. File: 2018-1663 NPA naloxone 9-26-2018.xlsx, 2018-1663 NPA opioids for naloxone ac.xlsx

Figure 5 below and Table 5 in Appendix B provides a ratio of naloxone prescriptions to opioid prescriptions dispensed from outpatient, mail-order, and retail pharmacies, by state, for the lower 48 contiguous states of the U.S. Of note, the ratio of naloxone prescriptions to opioid analgesics prescriptions seems to have increased in some specific states, namely Virginia and Vermont. Although the impact on dispensing was not formally studied, Virginia and Vermont were among the states that implemented “standing order” naloxone prescriptions in 2016 along with many other interventions throughout the U.S.ⁱ

Figure 5
Nationally Estimated Number of Naloxone Prescriptions per 1,000 Opioid Prescriptions Dispensed from U.S. Outpatient Retail Pharmacies in 2016 vs 2017 (48 contiguous)



Source: Symphony Health PHAST™ Prescription Monthly. January 2016–December 2017. Extracted October 2018. Files: 2018-1663 SHS FDA total naloxone by state 11-8-2018.xlsx; 2018-1663 SHS narcotic analgesic by state.xlsx

3.3 OTHER DISTRIBUTION PATHWAYS

ⁱ Washington Post. Virginia declares opioid emergency, makes antidote available to all. Gregory S. Schneider. November 21, 2016. Vermont Department of Health. Governor Shumlin announces all Vermont pharmacies can now sell naloxone without a prescription. Susan Allen. August 25, 2016.

FDA receives annual reports that include information on distribution of marketed drug products directly from Sponsors. Some Sponsors include in their reports stratification by donations and patient assistance programs (PAPs). Permission was received by Kaleo Inc., the manufacturer of the Evzio auto-injector, to disclose distribution information via these donation channels.

Between April 4th, 2016, and April 1st, 2017, Kaleo provided 33,377 packages (here a package consists of two auto-injectors) of Evzio at cost, and distributed 83,920 more packages for purchase through pharmacy distribution channels in the U.S. Kaleo also provided 273 packages through PAPs.ⁱⁱ

From April 4th, 2017, to April 3rd, 2018, Kaleo Inc. donated 28,274 packages of the 0.4 mg dose of Evzio through PAPs. Kaleo Inc. began commercially distributing Evzio 0.4 mg in July 2014 and then ceased commercial distribution in December of 2016. The last Evzio 0.4 mg PAP lot was distributed on December 15th, 2016, and the last Evzio 0.4 mg donation/free good lot was distributed on December 5th, 2017.ⁱⁱⁱ

Current annual distribution data have been provided by Kaleo in advance of annual report submission for this calendar year. Between October 19th, 2017 and October 18th, 2018, Kaleo donated 32,157 total packages of Evzio (2 mg) in the U.S. Kaleo reported 43,771 packages were made available through pharmacy distribution channels, and 1,545 packages were made available through PAPs.^{iv}

From November 18th, 2015, through November 17th, 2018, Adapt Pharma distributed 253,499 units (here a unit consists of two nasal sprays) of Narcan Nasal Spray according to their annual report data. Adapt did not specify pathways of distribution.^v

3.4 DRUG UTILIZATION SUMMARY

Findings from this review should be interpreted in the context of the known limitations of the databases used. This review provides drug utilization data for naloxone products sold and dispensed in the U.S. The data provided are meant to be contextual and background information for the advisory committee meeting discussion.

ⁱⁱ Kaleo Inc. Annual Report: Distribution Data. Food and Drug Administration, April 2017. Permission received November 2018

ⁱⁱⁱ Kaleo Inc. Annual Report: Distribution Data. Food and Drug Administration, April 2018. Permission received November 2018

^{iv} Kaleo Inc. Annual Report: Distribution Data. Food and Drug Administration, in submission. Permission received November 2018.

^v Adapt Pharma. Annual Report: Distribution Data. Food and Drug Administration, February 2017. Permission received November 2018.

Based on the IQVIA, National Sales Perspectives™, naloxone products were largely distributed to the non-retail setting of care, primarily to non-federal hospitals and clinics. These channels may also supply first responders (e.g., ambulances, other EMS), as well as community-based distribution programs, where transaction and utilization information are not routinely captured. Vials of injectable naloxone may be modified for use in the community via atomizers for nasal administration (e.g., kits distributed through harm reduction programs). Naloxone sales to retail pharmacies appear relatively small, but are increasing in recent years, with prescriptions dispensed from outpatient retail pharmacies also increasing, largely dispensed as the nasal formulation.

Innovative distribution mechanisms, such as state-based “standing order” naloxone prescriptions, may complicate the interpretation of the prescriber specialty data as one prescriber may account for all prescriptions dispensed under the standing order for a given state. Direct sales and donations from manufacturers are likely not captured in national estimates of sales obtained from proprietary sources, therefore sales data from these sources may underestimate the total availability of naloxone.

3.5 SUMMARY OF LITERATURE

In the US, there are currently three primary ways of obtaining naloxone:

- 1) Through a community-based organization
- 2) Through a prescription by a provider
- 3) Through a pharmacy-based provision^{vi}

These models of naloxone distribution may differ in who actually issues the prescription, but they overlap significantly with respect to the target populations (see **Table 2** below taken from Green et al, 2015)¹¹.

^{vi} Dispensed at a pharmacy without an individual prescription, generally through standing order prescription.

Table 2: Naloxone distribution models in the US (from Green et al, 2015)¹¹

	Community-based organization Naloxone distribution	Traditional prescription	Pharmacy-based Naloxone models			
			CPA	Standing medication order	Protocol order	Pharmacist prescribing
Who issues prescription?	Prescriber via standing order	Prescriber	Non-pharmacist prescriber	Non-pharmacist prescriber	Licensing board	Pharmacist
Medical professionals required	Varies by state: prescriber, state/local health department	Prescriber + pharmacist	Prescriber + pharmacist	Prescriber + pharmacist	Pharmacist	Pharmacist
Potential recipients	Individuals served by the community-based organization	Patients of the prescriber	Varies by state	Anyone meeting criteria specified by prescriber	Anyone meeting criteria specified by licensing board	Anyone for whom medication is indicated
Target overdose risk population served	People who use drugs (prescription opioids, heroin) who access the community-based organization*	People who use drugs who are in treatment/visit a prescriber*	People who use drugs (prescription opioids, heroin) who visit a pharmacy*	People who use drugs (prescription opioids, heroin) who visit a pharmacy*	People who use drugs (prescription opioids, heroin) who visit a pharmacy*	People who use drugs (prescription opioids, heroin) who visit a pharmacy*
		Patients prescribed opioids who are at risk of overdose*	Patients filling a prescription for opioids at a pharmacy who are at risk of overdose*	Patients filling a prescription for opioids at a pharmacy who are at risk of overdose*	Patients filling a prescription for opioids at a pharmacy who are at risk of overdose*	Patients filling a prescription for opioids at a pharmacy who are at risk of overdose*
Geographic reach	Limited to where community-based organizations are located and operate	Limited to where the prescriber practices	Any participating pharmacy within the state	Any participating pharmacy within the state	Any participating pharmacy within the state	Limited to where the pharmacist practices

*A majority of states now permit prescriptions to be written for third parties (e.g., friends, staff of organizations that provide services to individuals at risk of overdose) as well as the person at risk of overdose
CPA collaborative practice agreement

Despite the overlap, we tried to loosely organize published studies by program type and target population (3.5.1-3.5.3): community-based programs (3.5.1), prescribing programs (3.5.2.), and “take-home” naloxone programs for higher risk populations (3.5.3). We also summarize some simulation studies (3.5.4). We synthesized only the most relevant studies, below, and provided tables on reported naloxone dispensing and rescue attempts abstracted from the studies (note: the counts in the tables were adapted for the purposes of this review and only pertain to those who received naloxone). For Tables 3-5, it is not appropriate to aggregate counts of naloxone distributed or used across studies, to calculate the proportion of naloxone used from the total naloxone distributed, or to compare the amount of naloxone distributed or used between studies, as these data come from disparate convenience samples with limited or incomplete follow-up that differs between studies. In this analysis, we view these data as similar to published case reports; they capture distribution and utilization of community-use naloxone, and they are helpful informing further research. The data in Tables 3-5 are meant to provide context and describe reported use of naloxone as part of various distribution programs, not to make inferences about the effectiveness of a particular program or the comparative utilization in various populations.

See Appendix C for a detailed summary of all reviewed literature.

3.5.1 Community-based distribution programs outside of traditional health care settings

We defined this group of studies as those pertaining to overdose education and naloxone distribution (OEND) programs that use a diffuse network of organizations throughout a defined community for naloxone trainings, where naloxone is directly provided on-site. Some long-standing, well-known programs include the Chicago Recovery Alliance, the Drug Overdose and Prevention Education (DOPE) in San Francisco, Project Lazarus in

North Carolina, and the Massachusetts Department of Public Health OEND program. The makeup of the network of community-based organizations varies based on the program, but generally includes sites like social service agencies, HIV prevention and harm reduction organizations, community health centers and “safety-net” clinics, health departments, some medical facilities (e.g., emergency departments, urgent care centers), addiction treatment settings (inpatient, detox, and outpatient), homeless shelters, safe-injecting and needle/syringe exchange facilities, and community-based centers that hold support groups or other health-focused events. These OEND programs primarily target high-risk groups; however, they also train and distribute naloxone to any person in need, including lower risk people, and the friends/family of those at risk of overdose.¹²

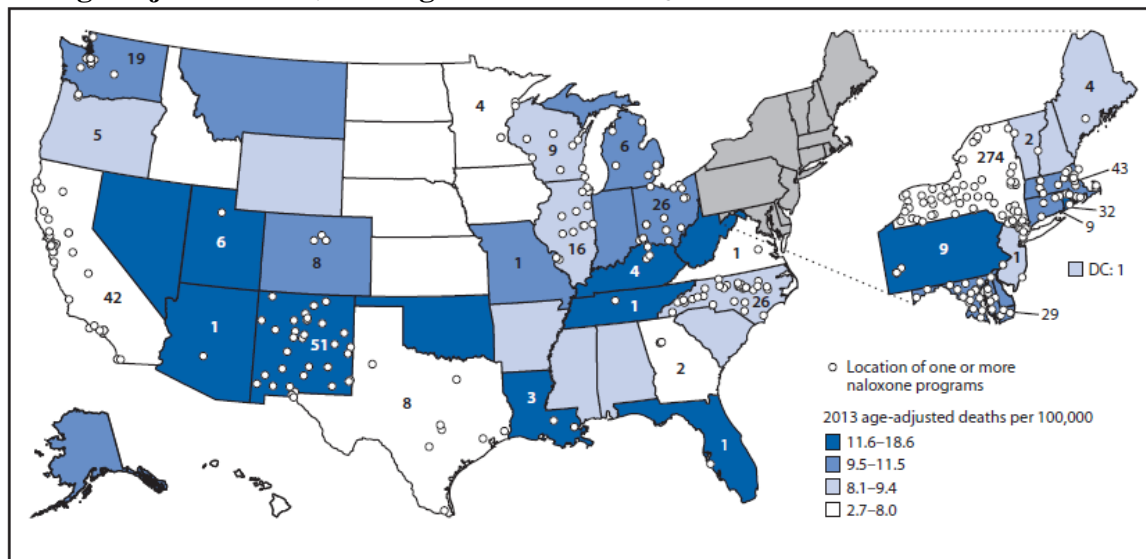
Table 3: Description of studies on community-based distribution programs

Author, year	Number of kits distributed or persons enrolled & trained (including only those who received naloxone kits)	Number of reported rescue attempts or naloxone administrations	Proportion (count) successful at preventing overdose death
Bagley, 2018 ¹²	40,801 people enrolled in Massachusetts programs from 2008-2015	4,373 people reported using naloxone	98.2% (4,229)
Bennett, 2012 ¹³	521 opioid users and 4 non-users drawn from community sites and incarcerated people set for release in Wales, in 2011	28 people reported using naloxone	95.4% (21 of 22 where outcome was known/collected)
Doe-Simkins, 2014 ¹⁴	4,926 enrollees with substance abuse histories at OEND community-sites in Massachusetts from 2006-2010	599 rescue attempts	97.2% (349 of 359 where outcome was known/collected)
Freeman, 2017 ¹⁵	2,910 naloxone kits distributed to community members in Alberta, Canada, from 2015-2016	472 rescue attempts	Not reported
Lewis, 2016 ¹⁶	113 people trained and followed -up with at community sites around Baltimore, MD, in 2014	3 people reported using naloxone	Not reported
Madah-Amiri, 2017 ¹⁷	411 people trained (and returned for follow-up) and 2,056 naloxone kits distributed from community sites in Oslo and Bergen, Norway, from 2014-2015	277 people reported using naloxone	100.0% (277 person-uses out of 277 where outcome was known/collected)
Rowe, 2015 ¹⁸	2,500 enrollees in the DOPE community-based harm reduction program in San Francisco, CA, from 2010-2013	702 reported rescue attempts	95.7% (692)
Rowe, 2018 ¹⁹	1,023 and 1,123 new enrollees in the DOPE community-based harm reduction program in San Francisco, CA, in 2014 and 2015, respectively	326 and 504 rescue attempts among all enrollees (new and continuing) in 2014 and 2015, respectively	Not reported
Walley, 2013 ²⁰	2,912 enrollees trained at sites around 19 different Massachusetts communities from 2006 - 2009	327 reported rescue attempts	98.0% (150 out of 153 where outcome was known/collected)
Wheeler, 2012 ²¹	53,032 people who were trained at 48 community-based distribution sites from 1996 to 2010 across the United States	10,171 reported rescue attempts	Not reported
Wheeler, 2015 ²²	152,283 people provided kits from 136 programs operating 644 community-based distribution sites from 1996 to 2014 across the United States	26,463 reported rescue attempts	Not reported
Winstanley, 2016 ²³	1,998 kits distributed from overdose prevention programs around Ohio, from 2012-2014	149 reported rescue attempts	Not reported
Yokell, 2011 ²⁴	10 people trained and follow-up with at an overdose prevention pilot program in Rhode Island, in 2006	5 people reported using naloxone	Not reported

While the types of programs differ with respect to the networks of community-based organizations involved in the distribution of naloxone, the data suggest that across both international (United Kingdom, Norway, Canada) and domestic (Ohio, Massachusetts,

California, Rhode Island, Maryland) locales, community-based OEND programs provide naloxone to people in need (including potential bystanders), and some of the naloxone is ultimately used in rescue attempts (e.g. the naloxone was administered, but may or may not have resulted in an opioid reversal) (See Table 3)^{vii}. As Wheeler, et al. 2015²² demonstrated, these types of programs are not confined to particular states, as community-based distribution programs have operated in many states dating back to 1996 (See Figure 5), resulting in over 26,000 reported rescue attempts nationwide by 2014 (See Table 3).

Figure 5 (taken from Wheeler et al 2015²²): Number* and location of local drug overdose prevention programs providing naloxone to laypersons, as of June 2014, and age-adjusted rates† of drug overdose deaths§ in 2013 - United States



* Total N = 644; numbers on map indicate the total number of programs within each state.

† Per 100,000 population.

§ CDC, National Center for Health Statistics; Compressed Mortality File 1999–2013 on CDC WONDER Online Database, released January 2015.

Many of these types of programs provide comprehensive training on how to identify an overdose, how to administer naloxone, and what to do after administering naloxone. This training may facilitate more effective use of naloxone in emergency situations; however, some data suggest that training does not necessarily improve outcomes with respect to successful naloxone administration.¹⁴ In many of the published studies, the reported rescue attempts were made by both those who received the naloxone, and by layperson bystanders. This suggests that the benefits of these programs extend beyond the naloxone recipient.

^{vii} Note: The data in this table are meant to describe naloxone use reported in the literature. We view these data similar to published case reports. These data should not be aggregated, and counts or proportions should not be used to compare across studies or populations since follow-up rates were generally poor, and differed by study.

Some ecological studies have shown that communities with greater access to OEND programs have better outcomes than those with less access. While these types of studies are challenged by secular trends in the measured outcomes, or other initiatives that could have impacted community-based outcome rates, they can be useful as hypothesis-generating. Walley et al.²⁵ conducted an interrupted time series analysis to evaluate the impact of state-supported OEND programs in 19 Massachusetts communities from 2006 - 2009. Compared to time periods when there was no implementation of OEND programs, communities in which 1-100 people per 100,000 population were engaged in OEND programs had a 27% [Confidence interval (CI): 9-43%] reduction in the rate of overdose mortality, and communities with >100 people per 100,000 population engaged in OEND programs had a 46% [CI: 24-61%] reduction in overdose mortality. In a study investigating the neighborhood-level correlates and spatial relationships of lay-person naloxone distribution and utilization and opioid overdose deaths from 2010 to 2012 in San Francisco, Rowe et al.²⁶ found that areas further from DOPE-led community distribution sites were associated with a 49% [CI: 33-61%] reduction in the rate of reversals per 500 meter increase in distance; however, different from Walley et al., proximity to distribution sites was not associated with reductions in opioid overdose death. Similarly, in a study²⁷ evaluating Project Lazarus in North Carolina, a statewide intervention designed to prevent opioid overdose, counties that had initiated policies promoting the distribution of naloxone saw no change in mortality, but a slight increase (9%, CI: 4-14%) in the rate of overdose-related emergency department (ED) visits from 2009 - 2014, after controlling for other county-level Project Lazarus interventions such as removing barriers to accessing MAT and limiting ED opioid analgesic prescribing. While the authors did not opine on why counties promoting naloxone use were associated with an increase in ED visits, we suspect that it could be due to the communication around naloxone use which encourages people to seek medical attention after naloxone is administered.

Overall, while data are limited with respect to the effectiveness of these community-based OEND programs, with much of the data coming from descriptive follow-up surveys of programs and those utilizing their services, the data suggest that these programs provide naloxone to those who need it, including family and friends in proximity to those at risk. Studies further suggest that some of the kits are ultimately used after distribution; some of the kits are used on those who received the naloxone, and some of the kits are used on others. That said, many of the studies were small, descriptive surveys of convenience samples that may lack generalizability to all community-based OEND program populations. These studies also generally relied on self-reported data without independent data verification, and thus may be impacted by misreporting. The total number of kits used or lives saved from OEND programs is unknown because much of the data on rescue attempts were collected when people came in for naloxone refills or as a part of follow-up by program staff; however, follow-up response rates were consistently low across these studies, and therefore, data on naloxone use and rescue attempts may be an underestimate. Additionally, successful programs with greater penetration in the community may report data more readily and may be accepted for publication more readily than less successful programs which could lead to publication bias.

Published ecological studies^{20,26,27} did not show consistent reductions in overdose mortality rates associated with community-level measures of “access” to OEND programs. Further research is needed to better understand whether communities are impacted by improved OEND program accessibility or community-based distribution.

3.5.2 Prescribing programs in health care settings

We defined this group of studies as those pertaining to programs housed in more traditional health care settings (primary care clinics, pain clinics, pharmacies, and opioid treatment programs including outpatient, inpatient detox, and methadone maintenance), where naloxone prescriptions can be provided to those prescribed opioid analgesics or opioids for MAT, such as methadone or buprenorphine, and assessment for additional prescriptions can be provided on a routine basis. Some of the naloxone prescribing programs designed for patients prescribed opioid analgesics are targeted to those deemed at high risk for overdose, such as those with substance abuse or opioid use disorder (OUD),²⁸⁻³⁰ while others offer naloxone to any patient prescribed opioid analgesics.²⁹⁻³³ In an opioid treatment program setting (MAT or otherwise), it is known that the patients may be at increased risk of overdose due to their substance abuse histories, and providing naloxone is considered a harm reduction measure designed to mitigate the effects of relapsing opioid abuse.

Table 4: Description of studies on prescribing programs

Author, year	Targeted patients: Opioid analgesic (OA), substance abuse or opioid use disorder (OUD), MAT patients (MAT)	Number of kits distributed or persons enrolled & trained (including only those who received naloxone kits)	Number of reported rescue attempts or naloxone administrations	Proportion (count) successful at preventing overdose death
Akers, 2017 ³⁴	OA + OUD	99 kits distributed from a pharmacy-based program for community use in Seattle, WA, from 20014-2016	20 reported rescue attempts	Not reported
Banjo, 2014 ³¹	OA + OUD	836 kits distributed to opioid analgesic patients, family of patients, and staff at health centers participating in a “take-home” naloxone program in British Columbia, Canada, from 2012-2013	85 reported rescue attempts	Not reported
Behar, 2016 ³⁰	OA + OUD	60 patients prescribed opioid analgesics or at risk of overdose at 6 safety-net health clinics in San Francisco, CA, from 2013-2015	3 people reported using naloxone	100.0% (3)
Han, 2017 ²⁸	OA + OUD	97 kits prescribed and dispensed to both opioid analgesic and substance abusing patients at three family health centers in Pennsylvania, from 2014-2015	5 rescue attempts	100.0% (5)
Katzman, 2018 ³⁵	MAT	215 patients in MAT for opioid use disorder who were trained and followed up with in a New Mexico opioid treatment program (OTP) in 2016	31 people reported 38 rescue attempts	100.0% (38)
Katzman, 2018 ³⁶	MAT	251 patients in MAT for opioid use disorder who were trained and followed up with in a New Mexico OTP in 2016	44 people reported 65 rescue attempts	100.0% (65)
Lopez-Gaston, 2009 ³⁷	OUD (in treatment, some MAT)	70 trained opioid users in outpatient treatment or recently discharged from inpatient treatment in the United	0 – no use	Not applicable

Author, year	Targeted patients: Opioid analgesic (OA), substance abuse or opioid use disorder (OUD), MAT patients (MAT)	Number of kits distributed or persons enrolled & trained (including only those who received naloxone kits)	Number of reported rescue attempts or naloxone administrations	Proportion (count) successful at preventing overdose death
		Kingdom in 2005		
Oliva, 2017 ²⁹	OA + OUD	39,328 Veterans Health Administration (VHA) patients prescribed opioids (n= 21,961) or with OUD (n= 8,925) across 142 VHA facilities nationwide from 2013 -2016	172 reported rescue attempts	Not reported
Strang, 2008 ³⁸	OUD (in treatment, some MAT)	186 trained opioid users in outpatient treatment or recently discharged from inpatient treatment in the United Kingdom in 2005	12 people reported using naloxone	100.0% (12)
Takeda, 2016 ³³	OA	164 patients prescribed opioid analgesics for chronic pain treated at a New Mexico pain clinic in 2016	0 – no use	Not applicable
Walley, 2013 ²⁵	OUD + MAT	1,553 enrollees trained at detox facilities, OTP clinics, and other sites around Massachusetts who had used methadone in the prior 30 days from 2008-2010	92 reported rescue attempts	Not reported

Among patients prescribed opioid analgesics, patients appear willing to receive naloxone prescriptions as a safety precaution, and despite some being at a perceived lower risk of overdose, the naloxone prescribed in those settings is occasionally used on the prescribed patients and/or their close contacts (See Table 4)^{viii}. However, in some of these studies it was not clear whether the naloxone prescribing was targeted based on clinical judgment of increased overdose risk from patients' opioid analgesic dose, current or past substance abuse histories, or other factors. Targeted prescribing³⁹ and “universal precaution” prescribing (e.g. prescribing to all patients regardless of perceived risk)³³ are fundamentally different models, and it appears that targeted prescribing may be more common in practice. This is evidenced in a study by Coffin et al.³² assessing

Figure 6 (taken from Albert et al, 2011): Project Lazarus co-prescribing priority groups

Naloxone priority groups and risk factors for opioid overdose
<ul style="list-style-type: none"> Recent medical care for opioid poisoning/intoxication/overdose Suspected or confirmed history of heroin or nonmedical opioid use High-dose opioid prescription (≥ 100 mg/day morphine equivalence) Any methadone prescription for opioid naive patient Recent release from jail or prison Recent release from mandatory abstinence program or drug detox program Enrolled in methadone or buprenorphine detox/maintenance (for addiction or pain) Any opioid prescription and known or suspected: <ul style="list-style-type: none"> Smoking, COPD, emphysema, asthma, sleep apnea, or other respiratory system disease Renal or hepatic disease Alcohol use Concurrent benzodiazepine use Concurrent antidepressant prescription Remoteness from or difficulty accessing medical care Voluntary patient request
ED = emergency department; COPD = Chronic obstructive pulmonary disease.

^{viii} Note: The data in this table are meant to describe naloxone use reported in the literature. We view these data similar to published case reports. These data should not be aggregated, and counts or proportions should not be compared across studies or populations since follow-up rates were generally poor and differed by study.

the effects of a policy change in six safety net primary care clinics in San Francisco from 2013 to 2015, where safety net clinic staff was provided education on naloxone co-prescribing. Over 38% (n=759) of patients received naloxone during the study period, and they were more likely to have had an opioid-related ED visit in the time prior to the study index date (before the clinic began naloxone co-prescribing), than those not receiving naloxone. At the same time, these patients were also less likely to have an opioid-related ED visit in the 12-months after the index date, but actual naloxone use was not assessed. Project Lazarus promoted a naloxone co-prescribing program in Wilkes County, North Carolina, identifying naloxone priority groups for co-prescribing (See **Figure 6**). This kind of prescribing prioritization is often used in some clinical decision making surrounding naloxone prescription.

There are instances when all patients have been prescribed naloxone independent of a risk assessment (“universal precaution model”), but no naloxone use was observed among those patients. Takeda et al.³³ conducted a prospective study at the University of New Mexico Pain Center looking at long-term outcomes associated with naloxone co-prescription, and provided naloxone training and education to a convenience sample of 164 consecutive patients treated with chronic opioid therapy. No overdose events occurred in the population, and no naloxone kits were used after one year of follow-up. In Han et al., 2017²⁸, while patients using opioid analgesics and patients suspected of substance abuse were both provided naloxone prescriptions, only patients prescribed naloxone because of their current substance use went on to use the naloxone.

In what may be the largest naloxone prescribing initiative of any major health system in the U.S. to date, the Veteran’s Health Administration (VHA) health system developed a national OEND program across all 142 VHA medical facilities.²⁹ The objective of this national program was to distribute naloxone to patients with opioid use disorder (OUD) and patients prescribed opioid analgesics, and implementing the program required key innovations including developing standard naloxone rescue kits, adding naloxone kits to the VHA national formulary, centralizing their distribution, and developing a clinical guidance for naloxone prescription, among others. The VHA has dispensed over 45,000 naloxone prescriptions to over 39,000 patients prescribed opioids or with OUD, with 172 reported opioid overdose reversals with VHA naloxone prescriptions through 2016. However, it was not clear what proportion of those reversals were in those prescribed opioid analgesics versus those with OUD, or whether some of the naloxone prescribing in patients using opioid analgesics was targeted based on clinical judgment as to the patient’s overdose risk.

Among those in treatment for OUD, including those on MAT, published data on co-prescribing/“take-home” naloxone programs suggest that, like patients using opioid analgesics, these patients also occasionally use the naloxone that is made available to them (See **Table 4**), often for overdose events among members of their immediate social networks.^{25,35,36,38}

Overall, data are limited on the utility of naloxone co-prescribing with analgesic or MAT opioids, particularly in the context of the “universal precaution model” where all patients are prescribed naloxone regardless of risk. Data suggest that some patients who are co-

prescribed naloxone do ultimately use it during overdose events, but it is not clear what proportion of the naloxone prescriptions are used on the patients themselves versus on those in proximity to the patients. Studies suggest that a potential residual benefit of co-prescribing naloxone to patients is the indirect access to naloxone among the patient's social network, as there are reports of naloxone rescue attempts by patients on friends, family, and acquaintances. Targeted co-prescribing also occurs, so teasing out what is confounding by indication in relation to who eventually uses the naloxone is challenging. Because the studies were mostly descriptive in nature, with limited and inconsistent follow-up, small convenience samples, and almost exclusively self-reported naloxone use, it remains unclear the extent to which naloxone co-prescribing, whether universal or targeted, is an effective strategy for reducing morbidity and mortality in patients. There are no known randomized studies that formally assessed outcomes associated with co-prescribing in patients prescribed opioid analgesics, those on MAT opioids, or those in treatment for OUD.

3.5.3 “Take-home” programs for higher risk populations

We defined this group of studies as those pertaining to “take-home” programs where one receives a naloxone kit at a single point in time, or without consistent or planned follow-up assessments for further naloxone dispensation. This category intersects with 3.5.1 (community-based distribution programs) and 3.5.2 (prescribing programs), but studies in this section exclusively focused on those at perceived high short-term risk for an overdose episode, groups generally lacking a long-term plan for care after naloxone is provided, specifically:

- those who were recently released from incarceration,
- those treated at an emergency department for an opioid overdose or adverse event,
- those presenting at needle exchanges, or with current injection drug use.

The OEND programs mentioned in section 3.5.1. are many of the same programs that facilitate provisional “take-home” naloxone to these groups, and therefore, many of the studies are like those mentioned in 3.5.1., with the same inherent caveats and limitations.

Table 5: Description of studies on “take-home” programs for higher risk populations

Author, year	Number of kits distributed or persons enrolled & trained (including only those who received naloxone kits)	Number of reported rescue attempts or naloxone administrations	Proportion (count) successful at preventing overdose death
Bennett, 2011 ⁴⁰	141 people trained and followed up with at a needle exchange center in Pittsburgh, PA, from 2005-2008	89 people reported using naloxone in 249 overdose events	96.0% (239)
Doe-Simkins, 2009 ⁴¹	278 people trained and followed up with at a needle exchange center in Boston, MA, from 2006-2007	50 people reported using naloxone	74 successful reversal attempts (denominator not reported)
Dong, 2012 ⁴²	50 people trained at needle exchange center in Alberta, Canada from 2005-2006	9 people reported using naloxone	Not reported
Dwyer, 2015 ⁴³	37 patients seen at an emergency department and deemed high risk due to their substance abuse in Massachusetts from 2011-2012	6 people reported using naloxone	Not reported
Enteen, 2010 ⁴⁴	1,942 enrollees in the DOPE program (recruited	399 rescue attempts	98.3% (357 of 363

Author, year	Number of kits distributed or persons enrolled & trained (including only those who received naloxone kits)	Number of reported rescue attempts or naloxone administrations	Proportion (count) successful at preventing overdose death
	from needle exchanges, and other higher risk venues) in San Francisco, CA, from 2003-2009		where outcome was known/collected)
Kan, 2014 ⁴⁵	951 people who inject drugs recruited from community sites and pharmacies in Kyrgyzstan and Tajikistan in 2011	589 rescue attempts	Not reported
Lankenau, 2013 ⁴⁶	30 people who inject drugs and who had recently witnessed an overdose (or had overdosed themselves) recruited from homeless service organizations in San Francisco, CA, from 2010-2011	17 people reported using naloxone	100.0% (29 of 29 where outcome was known/collected)
Leece, 2013 ⁴⁷	209 people trained at needle exchange center in Toronto, Canada, in 2011	17 rescue attempts	100% (17)
McAuley, 2010 ⁴⁸	19 opioid users (and a self-described “buddy”) who reported using opioids and were recruited by ambulance workers due to their acute overdose risk in Scotland, in 2009	3 people reported using naloxone	66.7% (2)
Nolan, 2017 ⁴⁹	88 participants in two prospective studies of people who inject drugs (with and without HIV) who had received “take-home” naloxone in Vancouver, Canada, from 2014-2015	18 people reported using naloxone	Not reported
Parmar, 2016 ⁵⁰	112 recently incarcerated people in England from 2012-2014	23 people reported using naloxone	Not reported
Piper, 2008 ⁵¹	122 people trained and followed up with at a needle exchange center in New York City, NY, in 2005	50 people reported using naloxone in 82 overdose events	100.0% (68 out of 68 where outcome was known/collected)
Tobin, 2009 ⁵²	85 trained and followed up with at a needle exchange center in Baltimore, MD, from 2004-2005	19 people reported using naloxone	Not reported
Wagner, 2010 ⁵³	47 people who inject drugs and were trained at a homeless service organization in Los Angeles, CA, from 2006-2008	22 people reported using naloxone in 35 overdose events	86.6% (26 out of 30 where outcome was known/collected)

Among people at acute risk where an immediate “take-home” naloxone supply is desired by the person or deemed appropriate given the circumstance, naloxone use is reported consistently across various populations and settings (see **Table 5**)^{ix}. There may be commonalities between programs, but each target population is unique, and “take-home” programs are designed to respond to the needs of these specific higher-risk groups. Based on the perceived urgency for a naloxone kit, targeting those with acute risk of overdose and those who may be in proximity to others at acute risk of overdose, may have a more meaningful, immediate impact on individuals and the community than targeting other groups potentially at risk^{40,50,51}, particularly in light of the recent rise in poisonings from fentanyl-containing drugs^{15,19,49}; however, while a reasonable assumption to make, there are no known data supporting this contention.

There are ecological data that may support policies targeting “take-home” naloxone provisions to high-risk patients. In 2011, Scotland implemented a national directive to supply “take-home” naloxone to high-risk patients, including those recently released

^{ix} Note: The data in this table are meant to describe naloxone use reported in the literature. We view these data similar to published case reports. These data should not be aggregated, and counts or proportions should not be used to compare across studies or populations since follow-up rates were generally poor and differed by study.

from prison and those discharged from the hospital. Bird et al.⁵⁴ conducted a study looking at the impact of the national policy on opioid-related deaths in the patients who were targeted. From 2006 to 2010, before implementation of the program, 9.8% (193) and 9.2% (181) of all opioid-related deaths (N=1,970) occurred in individuals who had been released from prison or discharged from the hospital, respectively, in the four weeks prior to their death. From 2011-2013, after program implementation, the rates were lower at 6.3% (76 out of 1212 total deaths) and 8.6% (105 out of 1,212 total deaths), respectively. As noted previously, ecological studies are susceptible to confounding by secular trends, and it is unclear whether that confounding impacted the findings of this study. A pilot study⁵⁰ randomizing recently-released incarcerated people to either “take-home” naloxone or standard of care had incomplete findings, but did show that larger randomized studies on the effectiveness of “take-home” programs for those at acute risk for overdose may be feasible.

Overall, the published studies suggest that providing “take-home” naloxone provisions to those at acute risk for overdose (e.g., recently released from incarceration, presenting at needle exchange centers, discharged from the emergency department or hospital after overdose) results in reversals. These studies were similar to the other descriptive survey studies discussed in 3.5.1 and 3.5.2, and most of the same limitations apply; however, these high-risk populations may be uniquely difficult to follow up for ascertaining rescue attempt information because of the circumstances surrounding their acquisition of the “take-home” provision, and therefore, data on actual naloxone use may be an underestimate.

3.5.4 Simulation studies

We identified several recently published studies using “real world” data and advanced analytical methods to help understand the potential impact of increased naloxone access. These types of studies used models imbued with various assumptions to simulate the effects of various naloxone-based initiatives and distribution scenarios at the community level. One study⁵⁵ used dynamic compartmental modeling to project opioid-related deaths and quality-adjusted life years from 2016 to 2025 after 11 theoretical policies were implemented, one of which was improving naloxone access. In this study, increasing naloxone availability resulted in the greatest number of deaths averted over the projected five-year and ten-year periods among all 11 studied policy interventions which included initiatives for reducing opioid analgesic prescribing, disposing of excess opioid analgesics, and expanding access to MAT. In another study⁵⁶, investigators used a sequential exploratory mixed methods design using qualitative data to inform an agent-based model with the objective of assessing the effectiveness of community-based naloxone distribution. Investigators found that having a single distribution site in a community would decrease overdose deaths by 8.3% relative to a baseline model with no distribution sites; adding secondary distribution through social networks to a single site resulted in 42.5% fewer overdose deaths relative to baseline. Other scenarios were also projected, relative to the baseline model: 1) a ten-fold increase in distribution sites distributing at least ten kits, but with no secondary distribution, resulted in a ~40% decrease overdose deaths, 2) combining secondary distribution with a ten-fold increase in

sites resulted in a 61.1% decrease in overdose deaths, and 3) adding distribution through a needle exchange site resulted in a 65% decrease in overdose deaths.

Concerns surrounding fentanyl overdose deaths motivated another study using data from British Columbia, Canada. In this study⁵⁷, investigators used a Markov chain model including data on opioid-related deaths, fentanyl-related deaths, ambulance-attended overdoses, and “take-home” naloxone program engagement to assess the impact of a “take-home” naloxone program between 2012 and 2016. They estimated that 298 (95% credible interval: 91-474) deaths were prevented by the program, with 226 (95% credible interval: 125-340) potentially prevented following the 2016 scale-up in naloxone kit distribution; counterfactual modelling showed that an additional 118 (95% credible interval: 64-207) deaths would have been prevented with an earlier scale-up in naloxone distribution.

Finally, in a study⁵⁸ investigating the benefits and cost-effectiveness of a naloxone distribution program in Connecticut, and the additional potential benefit of combining naloxone distribution with addiction treatment that may include access to HIV Pre-exposure prophylaxis (PrEP), a decision analytical Markov model was used to simulate opioid overdose death among people who inject drugs. Authors found that the naloxone distribution intervention alone (mainly from needle exchange sites) resulted in a >6% reduction in overdose death compared to no naloxone distribution at 5 years, 10 years, and 20 years post-intervention; naloxone distribution plus linkages to addiction treatment was associated with a 7.7%, 8.7%, and 9.8% reduction in mortality at 5, 10, 20 years, respectively. Naloxone distribution plus addiction treatment linkage with access to PrEP was estimated to have the biggest impact on overdose mortality at 5, 10 and 20 years (all over >21% reduction in mortality).

While these studies showed promising results with respect to the community effects of increasing naloxone access and distribution, the models employed came with some untestable assumptions and used only a limited number of “real-world” model inputs. Therefore, these findings should be viewed as hypothesis-generating. Future work is needed to see how well their model assumptions hold, and whether observational or randomized studies ultimately support their findings.

4 NALOXONE DATA SUMMARY

Over the last several years, sales of naloxone products from manufacturers through various channels of distribution have doubled, from 2.5 million units sold in 2013 to approximately 5 million units sold in 2017. The majority of sales of naloxone seem to be distributed to non-retail settings of care, such as non-federal hospitals and clinics, settings which may also supply emergency medical services. From 2016 to 2017, the number of prescriptions dispensed from U.S. outpatient retail pharmacies has more than doubled from approximately 134,000 to over 330,000. Naloxone access to the end-user occurs via a variety of pathways, some of which are not captured in available drug utilization data sources as these sources rely on transaction records from sales and prescriptions. Further, rescue kits distributed through harm reduction and patient assistant programs typically

contain modified devices that convert injectable vial formulations to formulations administered via the nasal route. These types of rescue kits may be the source of higher observed sales of injectable vial products compared to FDA approved nasal formulations and auto-injectors. Also, while naloxone prescriptions were most often written by mid-level practitioners (nurse practitioners and physician assistants) and generalists (family practice, general practice, and internal medicine specialties), “standing orders” for naloxone prescriptions may conflate rates of dispensing by certain specialties. This can occur if a state’s naloxone “standing order” is attributed to a health director in a general area of practice.

Published data on naloxone distribution programs can be organized into three broad, and somewhat overlapping categories: 1) community-based programs outside of traditional health care settings, 2) prescribing programs in health care settings, and 3) “take-home” naloxone programs for high-risk populations at acute risk of overdose. For the first group, data on community-based programs come from studies of OEND programs that use a diffuse network of organizations throughout a defined community for naloxone trainings, where naloxone is directly provided on-site. For the second group, data from prescribing programs come from programs housed in more traditional health care settings, where naloxone prescriptions can be provided to those also prescribed opioid analgesics, or MAT opioids, and assessment for additional prescriptions can be provided on a routine basis. For the third group, these studies focused on “take-home” naloxone programs designed for people who may be at acute risk for overdose (e.g., recently released from incarceration, presenting at needle exchange centers, discharged from the emergency department or hospital after an overdose event), where naloxone kits are distributed at a single point in time without planned follow-up assessments for further naloxone dispensation. Despite some differences in distribution modalities, particularly between community-based or “take-home” programs and prescription programs for patients using opioid analgesic or MAT opioids, all three categories of studies suggest that, regardless of the modality, programs offering naloxone provide naloxone to those who may or may not overtly express the need for it, and some of the naloxone is ultimately used in rescue attempts (e.g. the naloxone was administered, but may or may not have resulted in an opioid reversal). Evidence suggests a utility in naloxone access for a range of potential at-risk populations, including patient populations and those engaged in community programs. Rescue attempts were observed in both those dispensed/prescribed the naloxone, and in those proximal to those dispensed/prescribed the naloxone, such as friends, family, or acquaintances.

Community-based OEND programs have been operational across the U.S. since 1996, reporting thousands of rescue attempts from the naloxone they have distributed.²² In fact, some ecological studies have demonstrated that communities with greater access to OEND programs have more opioid overdose reversals and lower overdose mortality rates than communities with less access.^{20,26} Prescribing programs aimed at those prescribed opioid analgesics or MAT opioids, or those in treatment for substance use disorder, are generally designed as either targeted prescribing³⁹ or “universal precaution” prescribing (i.e., prescribing to all patients regardless of perceived risk)³³, and it appears that targeted prescribing may be more common in practice. The VHA health system has developed a

national overdose education and naloxone prescribing initiative across all 142 VHA medical facilities,²⁹ with the objective of distributing naloxone to patients with OUD, and to patients prescribed opioid analgesics. The VHA initiative is a useful case study for assessing outcomes associated with large-scale naloxone co-prescribing, as well as barriers and pitfalls around implementation of such a program. The effectiveness of this specific program is still under study, but there have been some reported opioid overdose reversals from veterans dispensed naloxone through this program. As a national program across a major health system, data from the VHA program can help elucidate the potential benefits and risks of both targeted and untargeted prescribing models.

Like community-based OEND and direct prescribing programs, targeted “take-home” naloxone programs designed for those at acute risk for overdose (e.g., recently released from incarceration, presenting at needle exchange centers, discharged from the emergency department or hospital for opioid overdose) also result in rescue attempts. While it is reasonable to assume that targeting those at acute risk of overdose may have a more meaningful, immediate impact on individuals and the community than targeting other groups, particularly in light of the recent rise in poisonings from fentanyl-containing drugs, there are no known data supporting this contention. Some ecological studies provided supportive evidence for targeting populations with acute risk of overdose for “take-home” naloxone provisions,⁵⁴ but further research is needed.

Overall, studies reporting on naloxone distribution from any modality (community-based OEND, direct prescribing programs, “take-home for acute risk) are very limited, with much of the data from small, descriptive surveys of convenience samples with often short and inconsistent follow up. It is unclear whether findings from these studies are representative of other similar programs, or programs in other geographic areas. Data on naloxone rescue attempts from studies of community-based or “take-home” programs generally relied on self-report, without independent data verification, and it was not clear how many kits were ultimately used or lives saved as these data were collected when people returned for naloxone refills, or when they were followed up with by program staff where follow-up response rates are routinely low. Therefore, data from these programs on actual naloxone use and opioid overdose reversals may be an underestimate. Even in studies of naloxone prescribing programs within more traditional health care settings where following up with patients was presumably easier, it was not always clear what proportion of the naloxone prescriptions were used on the patients themselves versus on those in proximity to the patients; this differentiation may further clarify the impact of implementing a prescribing program in practice. It can be difficult to tease out the effects of confounding by indication in relation to who ultimately uses the naloxone prescribed to them, as targeted prescribing, rather than “universal precaution” prescribing, appears to be more common. Additionally, across the published data on all potential populations there was a possible publication bias where only data from successful programs are ultimately reported in the literature.

The generalizability of these descriptive surveys is uncertain; however, in this analysis we viewed these data as similar to published case reports, capturing distribution and utilization of community-use naloxone, and helpful in informing further research on

naloxone use. There is still a clear need for improved survey studies with a complete accounting of all naloxone distribution and administration, but this is very unlikely given the indication for naloxone and the populations to which it is targeted. Also, randomized and/or prospective observational studies to better understand the relative effectiveness of various types of naloxone distribution programs, and how to maximize the potential impact of those programs for the patients and the community are warranted. In the absence of those data, studies using advanced modeling methods with “real world” data inputs may be helpful in generating hypotheses and informing future research efforts⁵⁵⁻⁵⁸.

The Agency is not aware of published opioid overdose mortality rates in specific sub-groups that may benefit from increased naloxone availability (e.g. patients with OUD or patients on MAT); therefore, estimating the potential impact of increased naloxone availability on any one specific sub-group is not appropriate.

5 CONCLUSIONS

Naloxone sales have increased in recent years, with the bulk of the sales going to non-retail settings, primarily hospitals and clinics, settings which may also supply emergency medical services. Although increasing, naloxone prescriptions dispensed from retail pharmacies account for a very small proportion of total naloxone available in the community. While studies are limited, evidence suggests that through all different modalities of naloxone distribution, across all populations, naloxone is used to reverse opioid overdose and to prevent overdose death in those provided the naloxone, and others around them. Various types of programs currently exist, including community-based programs, prescribing programs in more traditional health care settings, and programs aimed at those at acute risk of overdose. There is a need for improved understanding of the relative effectiveness of specific programs, and how best to maximize their impact in mitigating opioid overdose death.

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7 APPENDIX A: DRUG UTILIZATION DATABASE DESCRIPTIONS

IQVIA, National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IQVIA, National Prescription Audit™

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 – 75% (varies by class and geography) of mail service pharmacies and approximately 70 – 85% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

Symphony Health’s PHAST™ Prescription Monthly

Symphony Health’s PHAST Prescription Monthly is a syndicated view of U.S. retail, and mail order pharmacy prescription activity, updated on a monthly basis. PHAST Prescription Monthly covers over 54,000 retail pharmacies in the sample including mail order and specialty pharmacies. The dispensed prescriptions in the sample represent approximately 92% of all U.S. retail prescriptions

(cash, Medicaid, commercial) as well as 69% of all U.S. mail order prescriptions. The retail and mail order prescriptions are projected to the national level.

APPENDIX B: DRUG UTILIZATION DATA TABLES

TABLE 1

Nationally estimated number of units (e.g. vials, auto-injectors, nasal spray) of naloxone sold from manufacturers to U.S. channels* of distribution, 2013 - 2017

Channel	Product	2013		2014		2015		2016		2017	
		Eaches(N)	Share (%)	Eaches(N)	Share (%)	Eaches(N)	Share (%)	Eaches(N)	Share (%)	Eaches(N)	Share (%)
Grand Total		2,508,546	100%	3,171,030	100%	3,407,699	100%	4,487,344	100%	5,023,478	100%
Non-Retail	Total	2,449,938	97.7%	3,085,917	97.3%	3,240,311	95.1%	3,973,101	88.5%	4,181,254	83.2%
	Naloxone Inj	2,449,938	100.0%	3,085,739	100.0%	3,238,593	99.9%	3,826,995	96.3%	3,581,524	85.7%
	Nasal Spray	--	--	--	--	--	--	134,196	3.4%	595,924	14.3%
	Auto-Injector	--	--	178	0.0%	1,718	0.1%	11,910	0.3%	3,806	0.1%
Retail	Total	57,038	2.3%	82,766	2.6%	164,364	4.8%	505,302	11.3%	823,278	16.4%
	Nasal Spray	--	--	--	--	--	--	151,756	30.0%	468,092	56.9%
	Naloxone Inj	57,038	100.0%	79,670	96.3%	138,362	84.2%	267,340	52.9%	264,928	32.2%
	Auto-Injector	--	--	3,096	3.7%	26,002	15.8%	86,206	17.1%	90,258	11.0%
Mail	Total	1,570	0.1%	2,347	0.1%	3,024	0.1%	8,941	0.2%	18,946	0.4%
	Auto-Injector	--	--	32	1.4%	530	17.5%	2,970	33.2%	9,776	51.6%
	Nasal Spray	--	--	--	--	--	--	2,004	22.4%	4,792	25.3%
	Naloxone Inj	1,570	100.0%	2,315	98.6%	2,494	82.5%	3,967	44.4%	4,378	23.1%

Source: IQVIA, National Sales Perspective (NSP). January 2013 – December 2017. Data Extracted September 2018. File 2018-NSP naloxone 9-12-2018.xlsx.

*Non-retail channels include the following sub-channels non-federal hospitals, federal facilities, long-term care, HMOs, clinics, home health, and miscellaneous (including prisons and universities) Retail: includes chain, independent, food store, and mail service pharmacies.

TABLE 2

Nationally estimated number of naloxone prescriptions dispensed from U.S. outpatient retail pharmacies, stratified by product formulation, 2013-2017

Product	2013		2014		2015		2016		2017	
	TRx(N)	Share (%)	TRx(N)	Share (%)	TRx(N)	Share (%)	TRx(N)	Share (%)	TRx(N)	Share (%)
Grand Total	1,587	100%	6,579	100%	26,224	100%	134,102	100%	336,125	100%
Nasal Spray	--	--	--	--	--	--	48,123	35.9%	237,186	70.6%
Auto-Injector	--	--	1,366	20.8%	11,921	45.5%	47,043	35.1%	56,094	16.7%
Naloxone Inj	1,585	99.9%	5,210	79.2%	14,300	54.5%	38,936	29.0%	42,845	12.7%

Source: IQVIA, National Prescription Audit(NPA). January 2013 – December 2017. Data Extracted September 2018. File: 2018-NPA naloxone 9-26-2018.xlsx

TABLE 3

Nationally estimated number of naloxone prescriptions dispensed from U.S. outpatient retail pharmacies, stratified by prescriber specialty, 2017

Specialty	2017	
	TRx(N)	Share (%)
Grand Total	336,125	100%
Np-Pa*	100,600	29.9%
Fp-Gp-Im**	77,376	23.0%
Osteopathic Medicine	26,825	8.0%
Anesthesiology	21,543	6.4%
Physical Medicine & Rehab	17,918	5.3%
Pain Medicine	16,287	4.8%
Psychiatry	11,220	3.3%
Neurology	2,643	< 1%
Addiction Medicine	1,141	< 1%
All Other Specialties	60,572	18.0%

Source: IQVIA, National Prescription Audit(NPA). January 2017-December 2017.
 Data Extracted September 2018. File: 2018-1663 NPA naloxone 9-26-2018.xlsx
 *Np-Pa: Nurse Practitioner, Physician Assistant **Fp-Gp-Im: Family Practice,
 General Practice, Internal Medicine

TABLE 4

Nationally estimated number of naloxone and opioid analgesic prescriptions dispensed from U.S. outpatient retail pharmacies in 2016 and 2017 (48 contiguous states)

State	2016			2017		
	Naloxone (TRx)	Opioid (TRx)	Naloxone /1000 Opioid	Naloxone (TRx)	Opioid (TRx)	Naloxone /1000 Opioid
AL	1,741	5,868,405	0.30	3,908	5,374,347	0.73
AR	143	3,360,368	0.04	464	3,093,932	0.15
AZ	1,314	4,694,318	0.28	8,347	4,158,041	2.01
CA	11,434	17,724,349	0.65	14,728	15,861,173	0.93
CO	2,190	3,347,290	0.65	5,251	2,953,092	1.78
CT	5,368	1,963,843	2.73	5,372	1,733,677	3.10
DC	574	323,000	1.78	1,158	295,779	3.92
DE	106	612,700	0.17	450	510,910	0.88
FL	11,167	13,963,907	0.80	17,118	13,088,411	1.31
GA	2,352	8,116,203	0.29	3,097	7,606,725	0.41
IA	142	1,877,016	0.08	486	1,688,748	0.29
ID	303	1,378,631	0.22	588	1,273,727	0.46
IL	1,578	7,123,217	0.22	6,206	6,428,717	0.97
IN	1,756	5,450,849	0.32	4,545	4,896,016	0.93
KS	1,056	2,457,132	0.43	1,915	2,286,497	0.84
KY	3,022	4,198,732	0.72	6,791	3,878,271	1.75
LA	1,230	4,660,514	0.26	1,764	4,324,088	0.41
MA	9,124	3,321,592	2.75	14,069	2,908,470	4.84
MD	9,797	3,522,885	2.78	21,059	3,161,329	6.66
ME	353	861,520	0.41	1,031	743,442	1.39
MI	2,493	8,508,221	0.29	8,764	7,720,868	1.14
MN	919	2,558,883	0.36	2,386	2,239,063	1.07
MO	986	4,834,332	0.20	4,457	4,440,004	1.00
MS	221	2,982,315	0.07	1,247	2,668,828	0.47
MT	187	817,442	0.23	525	721,802	0.73
NC	14,753	8,202,643	1.80	21,032	7,297,453	2.88
ND	53	423,541	0.13	247	376,482	0.66
NE	113	1,252,267	0.09	314	1,123,487	0.28
NH	613	786,231	0.78	758	637,136	1.19
NJ	2,594	4,695,684	0.55	4,283	4,035,985	1.06
NM	2,210	1,267,656	1.74	5,048	1,104,564	4.57
NV	3,305	2,279,615	1.45	4,477	2,062,053	2.17
NY	5,423	8,787,889	0.62	8,057	8,083,664	1.00
OH	4,428	8,743,261	0.51	8,165	7,626,404	1.07
OK	4,188	3,824,024	1.10	7,257	3,531,671	2.05
OR	1,830	3,133,452	0.58	3,053	2,746,646	1.11
PA	8,584	9,243,012	0.93	22,465	7,944,263	2.83
RI	2,550	642,951	3.97	3,484	551,478	6.32
SC	1,198	4,174,726	0.29	2,772	3,798,663	0.73
SD	134	555,573	0.24	238	495,682	0.48
TN	5,289	7,348,011	0.72	14,254	6,643,113	2.15
TX	8,474	15,764,252	0.54	12,297	14,646,818	0.84
UT	4,276	2,190,226	1.95	6,388	1,993,520	3.20
VA	2,968	5,216,365	0.57	42,308	4,426,392	9.56
VT	271	385,149	0.70	3,413	315,479	10.82
WA	3,983	4,692,597	0.85	8,177	4,224,131	1.94
WI	1,747	3,346,367	0.52	5,465	2,838,077	1.93
WV	1,075	1,688,048	0.64	2,510	1,459,446	1.72
WY	137	388,281	0.35	469	353,700	1.33

Source: Symphony Health PHAST™ Prescription Monthly. January 2016-December 2017. Extracted October 2018.
Files: 2018-1663 SHS FDA total naloxone by state 11-8-2018.xlsx; 2018-1663 SHS narcotic analgesic by state.xlsx

APPENDIX C: LITERATURE REVIEW SUMMARY TABLE

(NOTE: PLEASE SEE TABLES 3-5 IN SECTION 3.5 OF THIS DOCUMENT FOR SPECIFIC DATA ON NALOXONE USE)

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
Community-based distribution programs outside of traditional health care settings					
Alexandridis et al.⁵⁹ A statewide evaluation of seven strategies to reduce opioid overdose in North Carolina 2018	Ecological study	North Carolina, 2009-2014. Project Lazarus was implemented in 74 of 100 counties beginning in 2013.	After adjusting for several Project Lazarus strategies, naloxone initiatives (broadly defined) were not associated with opioid overdose mortality (IRR 1.04, 95% CI: 0.94, 1.16), but they were associated with increases in ED visits (IRR 1.09, 95% CI: 1.04, 1.14).	Observational/ecological design precludes control of intervention allocation. Limited implementation period. Secular trends in the outcome rates may affect findings.	<i>The strategy evaluated in this analysis was limited to the development of policies to encourage take-home naloxone, not actual reversals, and thus may take longer to demonstrate an effect than the time period under analysis.</i>
Bagley et al.¹² Expanding access to naloxone for family members: The Massachusetts experience 2018	Retrospective, descriptive review of program data	Program participants (including concerned family members) were given overdose training and dispensed naloxone Massachusetts Overdose Education and Naloxone Distribution (OEND) program enrollee data, 2008-2015.	10,883/40,801 (27%) of OEND program enrollees were family members. Family members who reported substance use obtained naloxone most frequently at HIV prevention programs. Family members who did not report substance use obtained naloxone most frequently at community	All data on OEND program enrollees were based on self-report. Follow-up on naloxone use was not consistent across all participants and response rates were low. Reports of overdoses and reversals are subject to recall bias; under-	<i>The fact that trainees in this large cohort rescued a broader group of victims than they intended, supports wider naloxone rescue kit access to community members. [...] The experience in Massachusetts demonstrates that family members can be active participants in the</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
			meetings. Those who obtained naloxone as a family member performed 860 of 4,373 (20%) of total rescue attempts. Of these, 173 (20%) were actually performed on a family member.	reporting of naloxone use also possible.	<i>response to the overdose epidemic by attempting rescues of family members as well as non-family members.</i>
Bennett and Holloway¹³ The impact of take-home naloxone distribution and training on opiate overdose knowledge and response: An evaluation of the THN Project in Wales 2012	Survey of opioid users evaluating opioid overdose and naloxone education training, including knowledge of overdose and willingness to act	Wales, UK, beginning 2011. This program was implemented across Wales.	Significant increases in correct identification of risk factors for opioid overdose, and typical signs of overdose. Significant increases in confidence and willingness to administer naloxone and provide other first aid during overdose. Police and ambulance involvement was more common during overdoses in which naloxone was used by bystanders.	Rapidly expanding deployment of take-home naloxone (THN) during the study period may have also impacted outcomes in the comparison group of untrained study participants. Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.	<i>The evaluation report concluded that the outcome benefits of THN in Wales substantially outweighed the implementation drawbacks and recommended that the programme was expanded nationwide. The proposals were given the support of government ministers and the scheme was rolled out across Wales earlier this year.</i>
Doe-Simkins et al.¹⁴	Retrospective cohort study of an OEND	Massachusetts OEND program participants,	295 trained and 78 untrained OEND program	Untrained naloxone users were only	<i>We found few differences in behavior between</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
<p>Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study.</p> <p>2014</p>	program	2006-2010.	<p>participants (of 4,926 participants), reported performing 1 or more reversals for a total of 599 rescue reports.</p> <p>Trained and untrained participants reported no statistically significant differences in management of overdoses, including help-seeking behaviors and naloxone administration.</p>	<p>surveyed if they later participated in the OEND program.</p> <p>Reports of overdoses and reversals are subject to recall bias.</p> <p>Unclear whether study findings are generalizable to other OEND programs.</p>	<p><i>trained and untrained opioid overdose rescuers, which may warrant consideration of over-the-counter status for naloxone rescue kits in future prospective investigations.</i></p> <p><i>Randomized controlled trials or prospective cohort studies of OEND with systematic and thorough follow-up are the needed next steps in addressing the structure, content and optimal amount of training to accompany naloxone rescue kits and the effect of OEND on participant drug use</i></p>
<p>Freeman et al.¹⁵</p> <p>Alberta's provincial take-home naloxone program: A multi-sectoral and multi-jurisdictional response to overdose.</p>	Implementation study; descriptive survey of naloxone dispensing	Alberta's provincial THN program, late 2015-2016.	In the first year of implementation, 953 sites registered to dispense THN, 9,572 THN kits were distributed, and 472 reversals were reported.	<p>Not a formal outcome evaluation of the program.</p> <p>Counts of reversals based on self-report during return visits; under-reporting possible.</p>	<p><i>Though THN programs exist in many other jurisdictions, including other provinces in Canada, Alberta's THN program stands out due to its comprehensive, provincial scope and rapid scale-up.</i></p>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
2017					
Lewis et al.¹⁶ Evaluation of the Overdose Education and Naloxone Distribution Program of the Baltimore Student Harm Reduction Coalition	Implementation study; descriptive survey of naloxone dispensing	People attending OEND trainings in Baltimore, MD, and 10 additional Maryland counties. April-November 2014.	<p>285 community members trained, 250 kits distributed, 3 reversals reported. Among 132 trainees participating in the evaluation, participants demonstrated statistically significant increases in attitudes and self-efficacy related to overdose and naloxone distribution.</p> <p>Odds of perceived self-efficacy related to one's ability to administer naloxone higher post-training compared to pre-training.</p>	<p>Low response rate for 8-month follow-up.</p> <p>Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.</p>	<i>Trainings were effective in increasing self-efficacy surrounding overdose prevention and response, which appears to persist at up to 12 months following the training.</i>
2016					
Madah-Amiri et al.¹⁷ Rapid widespread distribution of intranasal naloxone for overdose prevention.	Implementation study; descriptive survey of naloxone dispensing	Multi-site OEND program in Norway, 2014-2015.	<p>2056 naloxone nasal sprays distributed across 20 participating sites; 277 successful reversals reported.</p> <p>Program achieved a target distribution rate of 144 kits per 100,000 population.</p>	Unclear generalizability to the US-based programs.	<i>We recommend a coordinated framework, aimed as a public health intervention, is best suited to potentially reduce the complex phenomenon of overdoses.</i>
2017					

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
Rowe et al.¹⁸ Predictors of participant engagement and naloxone utilization in a community-based naloxone distribution program 2015	Longitudinal survey study	DOPE Project participants in San Francisco, CA, 2010-2013.	DOPE trained 2500 participants and reported 702 reversals. Those who witnessed overdose (adjusted odds ratio (aOR): 2.02, 95% CI: 1.53-2.66; aOR: 2.73, 95% CI: 1.73-4.30) or used heroin (aOR: 1.85, 95% CI: 1.44-2.37; aOR: 2.19, 95% CI: 1.54-3.13) or methamphetamine (aOR: 1.71, 95% CI: 1.37-2.15; aOR: 1.61, 95% CI: 1.18-2.19) had higher odds of obtaining refills and reporting reversals, respectively.	Counts of reversals based on self-report during visits to DOPE program for naloxone refills. Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.	<i>We observed that participants who were of European background, had prior experiences with overdoses and used heroin or methamphetamine were more likely to return for refills and those who had prior experiences with overdoses and used heroin or methamphetamine were more likely to report reversals.</i>
Rowe et al.²⁶ Neighborhood-Level and Spatial Characteristics Associated with Lay Naloxone Reversal Events and Opioid Overdose Deaths 2016	Spatial, ecological study of opioid overdose deaths, reported naloxone reversals, and OEND site locations.	San Francisco, CA, 2010-2012.	Census tracts including or adjacent to OEND sites had statistically significantly higher income inequality, lower percentage black or African-American residents, more drug arrests, higher population density, more overdose deaths, and more reversals. Greater distance to nearest OEND site, was	Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. Missingness of location data for reported reversals may be problematic if not at random.	<i>This study affirms that locating lay naloxone distribution sites in areas with high levels of substance use and overdose risk facilitates reversals of opioid overdoses in those immediate areas but suggests that alternative delivery methods may be necessary to reach individuals in other areas with less concentrated risk.</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
			negatively associated with reversals (IRR 0.51 per 500m, 95% CI: 0.39-0.67) but not opioid overdose deaths.		
Rowe et al.¹⁹ Community-Based Response to Fentanyl Overdose Outbreak, San Francisco, 2015 2018	Survey of OEND responses to suspected white powder fentanyl appearing in San Francisco during the summer months of 2015.	DOPE Project participants San Francisco, CA, 2015.	In 2015, DOPE Project year-over-year registration increased 10%, naloxone refills 45%, reported reversals 55%. Opioid overdose deaths decreased 20% from 126 in 2014 to 101 in 2015. Fentanyl-involved deaths increased 38% from 8 to 11.	Only one sample of white powder was tested (though it was confirmed to be fentanyl). Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.	<i>Connections to social networks of people who use drugs can enhance surveillance and facilitate naloxone distribution and may reduce opioid overdose deaths.</i>
Walley et al.²⁰ Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis.	Interrupted time series analysis to evaluate the impact of state supported OEND programs on opioid overdose death in Massachusetts. OEND was implemented among opioid users at risk for overdose, social service agency staff, family, and friends of	19 Massachusetts communities (geographically distinct cities and towns) with at least five fatal opioid overdoses in each of the years 2004 to 2006. Among the 19 communities studied, none had any OEND implementation in 2002-05, 7 had some implementation in 2006	OEND programs trained 2,912 people who reported 327 naloxone rescues. The rescuer and the person who overdosed were usually friends. Naloxone was successful in 98% (150/153) of the rescue attempts. For the three rescue attempts where naloxone was not successful, the people who overdosed received care from the emergency	Collected participant-level data on those trained on OEND, and community-level data on changes in rates of overdose; unclear whether participation directly impacted rates in the community – ecological association. Ecological studies have limitations in that population-level	<i>This study provides observational evidence that by training potential bystanders to prevent, recognize, and respond to opioid overdoses, OEND is an effective intervention.</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
2013	opioid users. OEND programs equipped people at risk for overdose and bystanders with nasal naloxone rescue kits and trained them how to prevent, recognize, and respond to an overdose by engaging emergency medical services, providing rescue breathing, and delivering naloxone.	(median of 3 enrollees per 100,000 population), 14 had some in 2007 (median of 7 enrollees per 100,000), and all 19 had OEND implementation in 2008-09 (medians of 55 and 142, respectively).	<p>medical system and survived.</p> <p>Opioid related death rates were reduced in those communities that implemented OEND compared with community-year strata with no OEND implementation.</p> <p>In demographic, treatment utilization, and doctor shopping-adjusted (CII opioids from ≥ 4 prescribers and ≥ 4 pharmacies in a 12-month period) analyses of periods with and without OEND, communities with 1-100 per 100,000 engagement in OEND had a 27% (CI: 9%-43%) reduction in the rate of overdose mortality, and those with >100 per 100,000 engaged had a 46% reduction (CI: 24%-61%). There was no difference when looking at hospitalizations for overdose.</p>	outcomes may not reflect individual-level outcomes, and causality cannot be directly assessed or inferred; secular trends may also be an issue.	

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Wheeler et al.²¹ Community-Based Opioid Overdose Prevention Programs Providing Naloxone—United States, 2010 2012	Cross-sectional, online survey of known community-based OEND programs.	Community-based OEND programs in the United States, October 2010.	48 of 50 known programs responded from 15 states and DC. These programs reported training and distributing naloxone to an estimated 53,032 persons since 1996 (range: 0 to 16,220; median: 102.5; mean: 1,104.8). Programs reported 10,171 reversals with naloxone (range: 0 to 2,385; median: 32; mean: 211.9). In a recent 12-month period, programs distributed 38,860 vials of naloxone.	Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. OEND programs may not record naloxone use or opioid overdose reversals consistently or systematically.	<i>More noninjection opioid users might be reached by opioid overdose prevention training and (where feasible) provision of naloxone in jails and prisons, substance abuse treatment programs, parent support groups, and physician offices. Reaching users of prescription opioid analgesics is important because a large proportion of drug overdose deaths have been associated with these drugs.</i>
Wheeler et al.²² Opioid Overdose Prevention Programs Providing Naloxone to Laypersons — United States, 2014 2015	Cross-sectional, online survey of known community-based OEND programs.	Community-based OEND programs in the United States, October 2010.	136 of 140 known programs responded, from 84 community-based organizations, 18 health care facilities, 10 VA health care systems, 18 state or local health departments, and six pharmacies. These programs reported training and distributing naloxone to an estimated 152,283 persons since	OEND programs were identified by the Harm Reduction Coalition (HRC). Some programs may not have been known to HRC. Survey responses subject to biases within different OEND organizations. Reports of overdoses and reversals are subject to recall bias; under-	<i>This report suggests that many programs reach persons who witness heroin-related overdoses; additional methods are needed to provide naloxone kits to persons who might witness prescription opioid analgesic overdoses.</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
			1996 (range: 1 to 36,450; median: 100; mean: 1,120). Programs reported 26,463 overdose reversals (range: 0-5,430; median: 9; mean: 243). During 2013, 93 programs reported distributing or prescribing naloxone to 37,920 laypersons (range: 0 to 9000; median: 75, mean: 407.7). During 2013, 90 responding organizations reported distributing 140,053 naloxone vials (range: 1-53,200; median: 179.5; mean: 1,556.1).	reporting of naloxone use also possible. OEND programs may not record naloxone use or opioid overdose reversals consistently or systematically.	
Winstanley et al.²³ Barriers to Implementation of Opioid Overdose Prevention Programs in Ohio 2016	Cross-sectional survey of OEND programs.	OEND programs in Ohio, surveyed between August and October 2014.	20 of 22 identified programs responded, representing 17 cities, with the first opening in August 2012. 18 programs distributed naloxone overdose kits; programs had distributed a total of 1,998 kits, with 149 reversals reported. 16 programs provided additional addiction treatment and illicit drug services.	Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. OEND programs may not record naloxone use or opioid overdose reversals consistently or systematically.	<i>Rural and suburban OOPPs with naloxone distribution are particularly important as the average EMS response time is longer and not all first responders may carry naloxone.</i>

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Yokell et al.²⁴ Opioid Overdose Prevention and Naloxone Distribution in Rhode Island 2011	Implementation study; descriptive survey of naloxone dispensing	Preventing Overdose and Naloxone Intervention (PONI) program, Rhode Island, beginning late 2006.	120 participants trained to date. Limited data was available on reversals performed. 10 participants returned for follow-up and described using their training; 5 administered naloxone. PONI staff also reported training over 1,000 inmates on overdose prevention, recognition, and response. Clients were given 10ml multi-use vials of naloxone, enough for three reversals before needing to refill	Passive reporting of naloxone use and opioid overdose reversals; very low follow-up rate. Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.	<i>An ideal program would encourage physicians to prescribe naloxone in a proactive manner to appropriate at-risk patients, encourage the involvement of pharmacists and state policy makers, and allow community agencies to maintain OD prevention training and naloxone distribution programs with minimal programmatic support from the Department of Health.</i>
Prescribing programs in health care settings					
Akers et al.³⁴ Implementing take-home naloxone in an urban community pharmacy 2017	Process valuation of the first pharmacy-supported THN effort in the greater Seattle area.	A community pharmacy in Greater Seattle, WA area, 2012-2016.	Approximately 1400 individuals were trained. Pharmacy-based THN patients were older than THN patients obtaining naloxone through other programs. Patients tended to be bystanders. This pharmacy dispensed 234 kits directly in a 4-year period beginning	Multiple overlapping OEND interventions in Seattle make outcome evaluation of any one program challenging. (This team encouraged other pharmacies to adopt their model.) Reports of overdoses and reversals are subject	<i>Take-home naloxone programs can be successfully implemented into community pharmacies to increase access and awareness of opioid overdose recognition and response. There often may be stigma around opioid</i>

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			<p>August 2012.</p> <p>One partner organization reported 20 successful reversals reported based on 99 kits dispensed via this pharmacy. Another 505 kits were dispensed to King County as part of the county's OEND program.</p>	<p>to recall bias; under-reporting of naloxone use also possible.</p> <p>OEND programs may not record naloxone use or opioid overdose reversals consistently or systematically.</p>	<p><i>overdose and the patients that THN may attract. In our experience, we have had incredibly positive encounters with opioid users as well as their friends and family.</i></p>
<p>Albert et al.³⁹</p> <p>Project Lazarus: Community-Based Overdose Prevention in Rural North Carolina</p> <p>2011</p>	<p>Ecological, pre-post analysis of the implementation of Project Lazarus in a single county in North Carolina.</p>	<p>Wilkes County, a rural county in western NC, 2007-2009</p>	<p>The overdose mortality rate declined from 43/100,000py in 2008 to 29/100,000py in 2010, a ~33% reduction.</p> <p>This preliminary evaluation of Project Lazarus demonstrates the effect of multi-modal approaches in extremely motivated communities and institutions.</p> <p>Take-home naloxone was routinely prescribed by physicians to patients falling into 10 distinct risk groups (See Section 3.5 of this document)</p>	<p>Naloxone was investigated as a part of the larger Project Lazarus intervention. Multiple strategies were implemented simultaneously.</p> <p>The setting of the intervention has a somewhat higher prescription opioid analgesic-driven overdose death rate relative to the state, (NC) and nation.</p> <p>Limited implementation period.</p> <p>Secular trends in the outcome rates may</p>	<p><i>The provision of take-home naloxone acknowledges that prevention efforts can fail or take years to have effect and that overdose deaths can be prevented in the community. [...] The presence of a motivated community organizer, support from the medical establishment, and strong data utilization practices are key components for replication.</i></p>

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				affect findings.	
Banjo et al.³¹ A quantitative and qualitative evaluation of the British Columbia Take Home Naloxone program 2014	Cross-sectional evaluation of a provincial OEND program in Canada.	The British Columbia Take Home Naloxone (BCTHN) program, August 2012-March 2014.	<p>By early 2014, BCTHN had been implemented in 40 sites, trained 1318 participants, distributed 836 naloxone kits, and received 85 reports of overdose reversal. Detailed reports described 64 reversals.</p> <p>Naloxone was most commonly used on a third party (64.1%), in a private residence (67.2%), during overdoses involving heroin (93.8%) and fentanyl (18.8%), and most commonly resulted in no symptoms of withdrawal (45.3%), no aggression (64.1%), and 911 not being called (59.4%).</p>	<p>Unclear generalizability to the US-based programs.</p> <p>Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.</p>	<i>Stakeholder concerns and misconceptions should be addressed, and people who use opioids should be encouraged to contact emergency health care services during overdose events. Our findings highlight the success of the BCTHN program and suggest other communities across Canada should consider implementing THN programs to prevent harms from opioid overdoses.</i>
Behar et al.³⁰ Primary Care Patient Experience with Naloxone Prescription	Qualitative interviews with primary care patients who received naloxone prescriptions. (See Coffin, 2016, below.)	Patients in 6 safety-net primary care clinics who received naloxone prescriptions, San Francisco, CA, October 2013-October 2015. Patients reported on	Of 60 patients interviewed, 82% filled a prescription for naloxone, and 97% endorsed THN for patients prescribed opioids for pain. 57% reported a positive response to being offered	<p>Interviews only conducted in English.</p> <p>Small, qualitative survey of limited number of participants; unclear generalizability.</p>	<i>We found a naloxone prescription to be acceptable to primary care patients who are prescribed opioids. Most patients responded positively to being offered naloxone, and among</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
2016		substance use, perception of personal overdose risk, history of overdose, and experiences with THN.	THN, and 37% reported beneficial behavior change after receiving the prescription. 37% reported experiencing an opioid overdose, and 5% reported that THN had been used on them.	One patient refused naloxone, but research staff were instructed not to randomize this patient to interview.	<i>those with a negative reaction, all accepted the offer, and nearly all believed naloxone was appropriate for patients prescribed opioids. Since this project was initiated, the Food and Drug Administration has approved 2 naloxone products designed for layperson administration.</i>
Burrell et al.⁶⁰ The pharmacist's role in overdose: Using mapping technologies to analyze naloxone and pharmacy distribution 2017	GIS analysis of pharmacies providing OEND/THN in an urban area.	Allegheny County, PA, 2015.	28 of 322 active licensed pharmacies in Allegheny County were confirmed to carry and distribute naloxone. ZIP code tabulation areas (ZCTAs) with these pharmacies had above average overdose deaths compared to the entire county (7.38 vs 4.84) and higher rates as well (47.36 per 100,000 vs 38.38).	Cross-sectional, ecologic analysis limits causal inferences. ZCTAs do not describe real-world communities. THN-providing pharmacies may be undercounted.	<i>GIS mapping can be integrated into pharmacy practice to visually represent areas of need and available resources regarding opioid overdose.</i>
Coffin et al.³² Nonrandomized Intervention Study of Naloxone Coprescription for Primary Care	Nonrandomized, observational intervention study	6 safety-net primary care clinics in San Francisco, CA, February 2013-April 2014. 1,985 adults receiving long-term opioid therapy	38.2% of LTOT patients were prescribed naloxone. Patients prescribed higher doses of opioids and with past-year histories of opioid-related ED visits were more likely to be	Results may not generalize outside of safety-net clinic settings. Patients likely to have above-average rates of non-medical opioid use.	<i>In summary, we demonstrated that naloxone can be successfully prescribed to a substantial proportion of patients receiving opioids for chronic pain</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
Patients Receiving Long-Term Opioid Therapy for Pain 2016		(OTOT) were recruited.	<p>prescribed naloxone.</p> <p>Patients receiving naloxone had fewer opioid-related ED visits after 6 months (IRR: 0.53, 95% CI: 0.35-0.83) and 1 year (IRR: 0.37, 95% CI: 0.22-0.64) compared to those not receiving naloxone.</p> <p>No net change in opioid dose was observed. No statistically significant change in opioid poisoning mortality was observed over the study period.</p>	<p>Unable to ascertain whether patients filled naloxone prescriptions. Unable to ascertain healthcare received outside of safety-net clinics.</p> <p>Limited implementation period.</p>	<i>in primary care practices.</i>
Green et al.¹¹ Orienting patients to greater opioid safety: models of community pharmacy-based naloxone 2015	Case studies of pharmacy-based naloxone (PBN) via Collaborative Pharmacy Practice Agreements (CPAs) and Pharmacy Standing Orders.	A case study of CPAs in Rhode Island beginning 2011, and a standing order in Massachusetts beginning 2014.	<p>48 states permit CPAs, with 21 permitting pharmacists to initiate medication therapy under a CPA.</p> <p>Compared to CPAs, standing orders have broader “behind the counter” access that allow non-established patients to obtain naloxone at a pharmacy.</p>	<p>Challenging to evaluate the impact of these programs.</p> <p>Limited implementation period.</p> <p>Unclear generalizability to other regions</p>	<i>One of the largest barriers to expanded naloxone access is the medication's prescription status, which can only be changed by the Food and Drug Administration (FDA). Consequently, many of the recent efforts have involved changes to state law to permit naloxone to be distributed outside of the traditional prescriber-patient</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
			<p>PBN models need to address reimbursement concerns, namely consultation fees for pharmacists. PBN approaches such as CPAs and standing orders also require specific training and expertise for pharmacists.</p> <p>A naloxone CPA was approved in Rhode Island in 2011. Patients at a participating pharmacy with one of several eligibility criteria may be prescribed and dispensed naloxone by the pharmacist. 572 scripts were dispensed 2014-May 2015, 25% of all naloxone in RI.</p> <p>A naloxone standing order was adopted in Massachusetts, March 2014. A different law permits prescribing to likely bystanders. By December 2014, 145 retail pharmacies had filed a naloxone pharmacy standing order.</p>		<p><i>relationship.</i></p> <p><i>PBN may provide a pivotal foundation and catalyst for pharmacy-based services from which pharmacists can have more central roles as facilitators and advocates for treatment and recovery.</i></p>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
<p>Han et al.²⁸</p> <p>Naloxone Counseling for Harm Reduction and Patient Engagement</p> <p>2017</p>	Survey assessing the impact of naloxone training and dispensation using pre- and post-interviews of physicians and patients.	3 family health centers associated with the University of Pittsburgh Medical Center St. Margaret Family Medicine Residency Program, February 2014-May 2015.	<p>71 outreach letters were mailed or printed for patients, and 97 naloxone kits were dispensed. 60% of kits were prescribed for illicit opioid use, 36% for chronic pain treated with opioid analgesics, and 4% to concerned third parties. 5 reversals were reported by 16 patients who completed follow-up: all involved illicit opioid use and naloxone administration.</p> <p>Physicians reported statistically significant increases in comfort prescribing opioids for acute pain, and familiarity with prescribing naloxone for patients using MAT or illicit opioids. Physicians also reported that face-to-face naloxone counseling could improve satisfaction caring for new patients seeking chronic opioid refills (90%).</p> <p>On follow-up, patients reported high levels of</p>	<p>Low follow-up rate among patients; these patients may not be representative of all patients who received naloxone in this study.</p> <p>Unclear whether results are generalizable to other practices.</p> <p>Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.</p>	<p><i>We believe our interprofessional approach was foundational to successfully changing provider workflow and attitudes.</i></p>

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			comfort with discussing opioid use and drug abuse, administering and being administered naloxone, seeking opioid abuse services, and safety of chronic opioid therapy with naloxone.		
Katzman et al.³⁵ An Innovative Model for Naloxone Use Within an OTP Setting: A Prospective Cohort Study 2018	Pre-post surveys of opioid treatment program (OTP) patients. Enrolled subjects received THN and were followed up with after 3 months.	Patients enrolled in the University of New Mexico's Addiction and Substance Abuse Program (UNMASAP), recruited April 2016-July 2016, with follow-up at 3 months.	215 of 244 enrolled participants completed follow-up, with 31 reporting using their THN in 38 overdoses. All reversals were reported as successful, all involved heroin and people who inject drugs. Four participants performed multiple reversals (maximum of 4).	Reports of overdoses and reversals are subject to recall bias Unclear whether results are generalizable to other treatment settings.	<i>It appears that social contacts are a critical harm reduction component to the overdose reversals seen within the community associated with PWID. It is the authors' contention that take-home naloxone should be considered a necessary component of any federally qualified OTP program.</i>
Katzman et al.³⁶ Characteristics of Patients with Opioid Use Disorder Associated with Performing Overdose Reversals in the Community: An Opioid Treatment	Pre-post surveys of opioid treatment program (OTP) patients. Enrolled subjects received THN and were followed up with after 3 and 6 months.	Patients enrolled in the University of New Mexico's Addiction and Substance Abuse Program (UNMASAP), recruited April 2016-October 2016, with follow-up at 3 months.	251 of 287 enrolled participants completed 6-month follow-up (87% completion), with 44 reporting using THN in 65 overdoses. Two deaths among participants were not suspected to be opioid-related. Demographic factors associated with	Reports of overdoses and reversals are subject to recall bias. Unclear whether results are generalizable to other treatment settings.	<i>In this study, characteristics of OUD patients with significantly greater odds of performing naloxone OD reversals included: younger age, previously witnessing an opioid OD, receiving emergency room care for OD and having positive urine toxicology screens.</i>

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Program Analysis 2018			performing reversals identified 5 factors: history of ED care for overdose (OR: 4.89; 95% CI: 1.54-15.52), history of witnessing overdose (OR: 5.67, 95% CI: 1.24-25.87), testing positive for 2+ illicit substances at follow-up (OR: 5.26; 95% CI: 1.58-17.54) or missing urine testing at follow-up (OR: 3.46; 95% CI: 1.42-8.43) compared to negative urine test results, age less than 30 years compared to 45-79 (OR: 2.80; 95% CI: 1.02-7.66), and white/Hispanic (OR: 3.98; 95% CI: 1.41-11.21) race/ethnicity compared to white/non-Hispanic.		
Lopez- Gaston et al.³⁷ Can we prevent drug related deaths by training opioid users to recognise and manage overdoses?	Implementation study; pre-post surveys of patients with opioid dependence provided OEND.	Patients with opioid dependence who were given OEND, Birmingham and London, UK, January 2006-January 2007	70 patients were provided OEND, with 83% and 70% completing 3- and 6-month follow-up. While the overall cohort demonstrated retained knowledge of overdose signs across the follow-up period, those who retained their THN at 6	Small sample with unclear representativeness to other patients with opioid dependence; unclear generalizability to the US-based programs. Reports of reversals	<i>Our findings confirm that training of drug users constitutes a valuable resource in the management of opiate overdoses and growth of peer interventions that may not otherwise be recognised or addressed. Obstacles have been</i>

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2009			<p>months had statistically significantly higher knowledge of opioid overdose signs compared to those who had lost their THN.</p> <p>At 6 months, 30 of 37 participants kept naloxone at home only. In the 5 cases analyzable, no participants used their THN.</p>	from brief informal follow-up phone interviews in some cases; subject to recall bias.	<i>identified at individual (transportability, stigma) and at a systems level (police involvement, prescription laws). Training individuals does not seem to be sufficient for these programmes to succeed and a coherent implementation model is necessary.</i>
Oliva et al.²⁹ Opioid overdose education and naloxone distribution: Development of the Veterans Health Administration's national program 2017	Process evaluation of national OEND program deployment within the Veterans Health Administration (VHA)	All VHA facilities (n=142). OEND program implementation began April 2013 and was fully implemented by November 2015.	<p>Through FY 2016, VHA dispensed 45,178 naloxone prescriptions written by 5693 prescribers to 39,328 patients who were primarily prescribed opioids or had opioid use disorder.</p> <p>As of February 2016, there were 172 spontaneously reported opioid overdose reversals with the use of VHA naloxone prescriptions.</p>	<p>Authors' note this is not an outcome evaluation of the VHA OEND program.</p> <p>Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.</p>	<i>VHA has successfully translated community-based OEND into health care system-based OEND targeting 2 patient populations.</i>
Strang et al.³⁸ Overdose training and take-home	Pre-post surveys of OEND participants, including 3-month follow-up.	People who use opioids recruited from 20 drug services in England, including in- and	Participants (n=239) demonstrated increased awareness of overdose risk factors, signs,	Unclear whether results are generalizable to other treatment settings, or US-based settings.	<i>With overdose management training, opiate users can be trained to execute</i>

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naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses 2008		outpatient services and criminal justice intervention programs, 2005-2006.	response, and willingness to act immediately after training. 186 of 239 participants (78%) completed 3-month follow-up, and 18 participants reported 17 overdoses, with naloxone used in 12. One death occurred among the 6 cases where naloxone was not used.	Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.	<i>appropriate actions to assist the successful reversal of potentially fatal overdose. Wider provision may reduce drug-related deaths further.</i>
Takeda et al.³³ Coprescription of naloxone as a universal precautions model for patients on chronic opioid therapy-observational study 2016	Prospective observational study of OEND in a clinical setting.	164 patients (18 or older) treated with chronic opioid therapy (COT) for noncancer pain at the University of New Mexico Pain Center, Albuquerque, NM, through early 2016. OEND was provided to all eligible participants and caregivers.	No overdoses occurred in the study population, and no kits were used after 1-year of follow-up.	Small sample recruited from a specialty clinic; unclear generalizability.	<i>One reason why our study cohort did not use the naloxone kit may be because the health care providers at the UNM Pain Center always use screening tools, controlled substance agreements, and are very careful about the monitoring of opioid use.</i>
Walley et al.²⁰ Opioid overdose prevention with intranasal naloxone among people who take	Follow-up survey after OEND implementation in a methadone-using population.	Patients recently taking methadone in a variety of settings including methadone maintenance treatment programs (MMTPs), inpatient detoxification, and HIV	1553 participants received OEND. Participants reported 92 rescues involving naloxone. Of these, at least 90% involved heroin, while 4.8% involved	Limited follow-up period; OEND efforts began in September 2006, though data collection only began in September 2008.	<i>This study demonstrates OEND can be implemented among people who take methadone in numerous settings, including MMTPs, detox programs,</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
methadone 2013		prevention programs, Massachusetts, 2008-2010. Other settings included residential and intensive outpatient treatment, emergency departments, community meetings, homeless shelters, etc.	methadone. Reversals were most common among HIV prevention program participants (7.6% of enrollees reporting reversal), followed by MMTPs (3.0%), inpatient detox (2.9%), and all other settings (2.4%).	Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.	<i>HIV prevention programs, community meetings, other outpatient and residential addiction treatment programs, emergency departments, and homeless shelters.</i>
“Take-home” programs for higher-risk populations					
Bennett et al.⁴⁰ Characteristics of an Overdose Prevention, Response, and Naloxone Distribution Program in Pittsburgh and Allegheny County, Pennsylvania. 2011	Implementation study; survey of program participants	OEND program within an Allegheny County, PA needle exchange, 2005-2008.	89 of 426 participants reported 249 overdose events where naloxone was used. Two events resulted in death; 96% of events resulted in a successful reversal.	Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. Unclear whether findings are generalizable to other regions.	<i>Our data support the findings of other studies that have examined naloxone training and prescription programs in other regions, namely that these programs can be implemented to serve drug-using communities who report being able to use naloxone in overdose situations with few negative consequences, including death.</i>
Bird et al.⁶¹ Effectiveness of Scotland's	Ecological study.	Opioid related deaths (ORDs) in Scotland (overall), and ORDs who were released from prison	From 2006-2010 (prior to the national naloxone policy), 9.8% (193/1970) of all ORDs were released	Unclear if decedents were given naloxone. The beneficiary of	<i>With 2 years of Scotland's National Naloxone Programme to follow, the current data</i>

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National Naloxone Programme for reducing opioid-related deaths: a before (2006–10) versus after (2011–13) comparison 2015		and released from the hospital, 2006-2013, with the National Naloxone Program beginning January 2011. Scotland's program included all prisons.	<p>from prison in the 4 weeks prior to their death, and 19% (374/1970) were released from prison <u>or</u> were released from the hospital 4 weeks prior to their death.</p> <p>From 2011-2013 (after the national policy was adopted), 6.3% (76/1212) of all ORDs were released from prison in the 4 weeks prior to their death, and 14.9% (181/1212) were released from prison <u>or</u> were released from the hospital 4 weeks prior to their death.</p> <p>These reductions were statistically significant.</p>	<p>THN-on-release is not typically the person released from prison (see Parmar et al. 2017).</p> <p>Ecological, pre-post studies have limitations in that population-level outcomes may not reflect individual-level outcomes, and causality cannot be directly assessed or inferred; secular trends may also be an issue.</p>	<i>suggest at least 20% and best estimate of 36% reduction in prison release ORDs, which may be due directly to the programme.</i>
Doe-Simkins et al.⁴¹ Saved by the Nose: Bystander-Administered Intranasal Naloxone Hydrochloride for Opioid Overdose. 2009	Implementation study; survey of program participants	OEND program within a Boston, MA needle exchange, 2006-2007.	50 of 385 participants reported 74 successful opioid overdose reversals.	<p>Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.</p> <p>Unclear whether findings are generalizable to other regions.</p>	<i>Overdose prevention education with distribution of intranasal naloxone is a feasible public health intervention to address opioid overdose.</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
Dong et al.⁴² Community-based Naloxone: A Canadian Pilot Program 2012	Implementation study; survey of program participants.	Convenience sample of 50 needle exchange participants in Edmonton, Alberta, recruited 2005-2006.	78% of participants had a history of overdose, 92% had witnessed overdose. Naloxone use was reported 9 times, with no deaths reported.	<p>Small, convenience sample design (lack of control group).</p> <p>Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.</p> <p>Unclear whether findings are generalizable to US-based programs.</p>	<i>These programs have the potential to reduce overdose deaths and drug use among trained participants. Further study and more systematic tracking of participants and outcomes are needed.</i>
Dwyer et al.⁴³ Opioid Education and Nasal Naloxone Rescue Kit Distribution in the Emergency Department 2013	Retrospective survey of Emergency Department (ED) patients receiving overdose education (OE) with and without naloxone distribution.	ED patients at Boston Medical Center, a Level I trauma center, January 2011-February 2012.	<p>51 of 415 subjects completed the survey an average of 11.8 months after their ED visit.</p> <p>Among 27 who witnessed an overdose, 63% called 911, 26% performed rescue breathing, 22% administered naloxone. Those either dispensed naloxone in the ED or obtaining naloxone elsewhere were more likely to perform a life-saving measure compared to those only given OE (84% vs. 38%, $p<0.05$).</p>	<p>Low response rate. Investigators used administrative ED data to contact patients by phone.</p> <p>Patients were not randomized; unclear what mechanism was used to decide whether patients either received OEND or OE only.</p> <p>Reports of overdoses and reversals are subject to recall bias.</p> <p>Pilot study, unclear whether findings are</p>	<i>While this was a pilot study using retrospective methods, it is the first description of an ED-based OD prevention program that includes naloxone distribution and supports the need for further OEND study and implementation efforts in EDs.</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
				generalizable to settings/programs, and other regions.	
Enteen et al.⁴⁴ Overdose Prevention and Naloxone Prescription for Opioid Users in San Francisco 2010	Implementation study; survey of OEND program participants.	People who inject drugs (PWID) participating in the Drug Overdose Prevention and Education (DOPE) Project, San Francisco, CA, 2003-2009.	Of 1,942 participants trained and prescribed naloxone, 215 (11%) reported administration during a total of 399 overdose events.	Follow-up limited to only those who returned for naloxone refills. Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. Unclear whether findings are generalizable to other regions.	<i>Participation has grown steadily among individuals at high risk of witnessing overdose events, and findings indicate that participants are motivated to receive refills following naloxone loss or use. Among trained participants who report using naloxone, nine in 10 report positive outcomes.</i>
Kan et al.⁴⁵ Effective use of naloxone among people who inject drugs in Kyrgyzstan and Tajikistan using pharmacy- and community-based distribution approaches. 2014	Implementation study; surveys of program participants.	People who inject drugs participating in pilot THN programs in Kyrgyzstan and Tajikistan, beginning 2011.	High proportions of respondents in both Kyrgyzstan and Tajikistan reported experiencing (51%, 92%) and witnessing (83%, 100%) overdose, and high proportions reported being injected with (82%, 59%) and injecting others (83%, 51%) with naloxone. Estimates of naloxone wastage were at 4-14%, depending on the country	Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. Unclear whether findings are generalizable to US-based programs. Wastage model results likely do not generalize to US. Selection bias likely among program	<i>Introduction and expansion of the naloxone distribution programs in the Central Asian Republics leads to proficient use of this life-saving product by PWID and those who become overdose witnesses, and that a large proportion of PWID who receive naloxone are using it to save lives by reversing opioid overdose.</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
				participants.	
Lankenau et al.⁴⁶ Injection drug users trained by overdose prevention programs: Responses to witnessed overdoses 2013	Qualitative, interview-based study.	A sample of PWID with a history of witnessed overdose recruited from two community-based organizations providing OEND in Los Angeles, CA, 2010-2011.	Of 30 recently witnessed overdoses, recovery occurred in 29, and naloxone was used in 15. Participants reported feeling capable of injecting naloxone.	Interviews focused on most recently witnessed overdose event; still subject to recall bias. Participants had to be return visitors to OEND sites.	<i>The authors conclude: IDUs who are trained by OPPs report successfully responding to drug overdoses – no participants in this study reported that an overdose victim died.</i>
Leece et al.⁴⁷ Development and Implementation of an Opioid Overdose Prevention and Response Program in Toronto, Ontario 2013	Implementation study; descriptive survey of naloxone dispensing	People who use opioids trained by the Prevent Overdose in Toronto (POINT) OEND program, Toronto, Ontario, 2011-2012.	209 clients were trained in the first 8 months of the program, reporting 17 administrations of naloxone.	Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. Unclear whether findings are generalizable to US-based programs.	<i>The initial development and implementation experiences of the POINT program – and its potential to save lives – are encouraging. Recruitment has exceeded expectations, and the program has enjoyed a positive community reception.</i>
McAuley et al.⁴⁸ Responsible management and use of a personal take-home naloxone supply:	Pilot intervention study. Clients attended OEND training with an overdose rescue “buddy” as a condition for receiving naloxone.	Lanarkshire, Scotland, years unknown.	19 clients issued naloxone; 2 reversals reported. One death witnessed by client who did not have naloxone on hand at time.	Several program stipulations reduce generalizability to other OEND programs and settings. Notable pre-training	<i>Our model has shown the potential for a small sample of drug users to manage their own THN supply responsibly.</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
A pilot project 2010			<p>15 clients confirmed to have their kit after 6 months of follow-up.</p> <p>Knowledge and confidence scores were higher at 2- and 6-month follow up compared to pre-training scores.</p>	<p>dropout of potential clients.</p> <p>Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.</p> <p>Unclear whether findings are generalizable to US-based programs.</p>	
Nolan et al.⁴⁹ Awareness, Possession, and Use of Take-Home Naloxone Among Illicit Drug Users, Vancouver, British Columbia, 2014-2015 2017	Cross-sectional analysis of two prospective cohorts of people who use drugs: (the Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS))	People who use drugs, including non-opioids, Vancouver, British Columbia, December 2014-May 2015.	<p>Of 1137 participants, 727 reported lifetime overdose, 220 had recently witnessed overdose. 769 were aware of THN, though only 88 of 392 opioid users (22%) had a THN kit.</p> <p>In a final model, factors associated with THN possession included younger age (aOR: 1.04 per year, 95% CI: 1.01-1.06), daily or more frequent heroin injection (aOR: 1.31, 95% CI: 0.79-2.17), and ever witnessing overdose (aOR: 1.85, 95% CI: 1.11-3.06).</p>	<p>The 2 cohorts used only include Vancouver PWUD; the BC THN program is provincial. High rates of HIV, HCV, and drug injection.</p> <p>Potential for unmeasured confounders, social desirability bias, reverse causation.</p> <p>Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible.</p> <p>Unclear whether</p>	<i>Overdose prevention education programs for PWUD should be expanded to include a strategy for accurate risk assessment of not only personal risk for overdose (particularly among people who inject drugs).</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
				findings are generalizable to US-based programs.	
Parmar et al.⁵⁰ Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths 2017	Randomized controlled (pilot) trial of OEND upon release from incarceration. The trial was stopped early based on parallel results from Scotland (see Bird et al. 2016).	Recently incarcerated being released from 16 prisons in England, May 2012-December 2014.	Of 1685 recently incarcerated and randomized to either THN or control package, 218 returned questionnaires, 205 with exposure assignment (112 naloxone, 93 controls). 80 (71%) reported naloxone carriage; 23 (21%) reported naloxone administration (vs. 9% for controls); 137 (67%) reported heroin use in first two weeks post-release. Of 4 opioid-related deaths, 2 had received naloxone, though 3 had been randomized to receive it.	The trial was abandoned early because interim analyses showed that use of naloxone on others was common (~3:1 vs self), which greatly diminished power to reduce overdose death among prisoners. All participants began receiving THN at the end of randomization. Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. Unclear whether findings are generalizable to US-based programs.	<i>Our findings add trial-based evidence to the growing consensus that pre-provision of take-home emergency naloxone can enable life-saving interim measures to prevent overdose deaths, and that the period after prison release is not only a time of great concentration of such deaths but also of opportunity to prevent this major contribution to the global burden of disease.</i>
Piper et al.⁵¹ Evaluation of a Naloxone	Evaluation of the Skills and Knowledge on Overdose Prevention (SKOOP)	People who inject drugs in New York City, 2005.	122 participants in SKOOP reported administering naloxone 82 times, with 68	Authors note that participants in OEND such as SKOOP are self-selected and may be	<i>This evaluation of naloxone administration suggests that drug users can be trained to respond</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
Distribution and Administration Program in New York City 2008	program; survey of program participants.		successful reversals and the remaining 14 unknown. 82% of respondents reported feeling comfortable using naloxone; 86% reported wanting naloxone if overdosing.	more motivated than other groups. Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. Unclear whether findings are generalizable to other regions.	<i>to heroin overdose by giving naloxone and that naloxone administration by drug users can save lives.</i>
Samuels et al.⁶² Emergency department-based opioid harm reduction: Moving physicians from willing to doing 2016	Cross-sectional web-based survey of ED physicians from 3 tertiary referral centers in 2013. Objective was to measure impact of physician knowledge attitudes confidence and self-efficacy on willingness to perform opioid harm reduction (OHR) interventions including opioid overdose education; naloxone prescribing; and referral to naloxone, methadone,	200 physicians completed the survey. 180 surveys were fully completed.	Stepwise linear regressions showed positive correlation between attitude, confidence, self-efficacy, and professional impact factors. Overall willingness as a composite factor explained variance in physician willingness for OHR. Survey respondents were overall willing to perform OHR interventions in the ED (mean: 3.81, 95% CI: 3.72-3.91), but they lacked confidence in	Authors admit that response rates varied by site, ranging from 53.7% to 89.5%. Survey conducted at three hospitals; unclear whether findings are representative of other hospitals, or regions. Voluntary survey may create a participation bias (selection bias). Respondents willing to perform OHR, but few actually do.	<i>Possible knowledge gaps include skills-based knowledge about addiction and overdose counseling; knowledge of available community resources; evidence supporting OHR interventions; and indications, formulations, and dosing for prescription naloxone. Physicians are willing to perform OHR interventions, and we have identified time, knowledge, training, and institutional support as critical barriers that need</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
	and syringe access programs. Used principal component analysis to focus on 5 component factors: 1) attitude, 2) confidence 3) self-efficacy, 4) professional impact factors, and 5) personal impact factors		<p>performing many of tasks, particularly referring to a community naloxone program (mean: 2.66, 95% CI: 2.48-2.84), writing a prescription for naloxone (mean: 2.52, 95% CI: 2.34-2.69), and referral to a syringe access program (mean: 2.77, 95% CI: 2.60-2.95).</p> <p>Physicians reported significant impact of professional factors on whether they would prescribe naloxone, refer to a naloxone program, or refer to a syringe access program (mean: 4.25, 95% CI: 4.18-4.32). Personal experience with someone with an addiction had less of an impact (mean: 3.54, 95% CI: 3.39-3.70). Respondents considered lack of time (mean: 2.89, 95% CI: 2.73-3.05), training (mean: 3.14, 95% CI: 2.92-3.36), knowledge (mean: 3.08, 95% CI: 2.89-3.27), and institutional support</p>		<i>to be addressed to convert willingness to practice and must be considered in the design of any ED-based naloxone initiative.</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
			(mean: 2.84, 95% CI: 2.65-3.03) as prohibitive barriers to naloxone prescribing.		
<p>Samuels et al.⁶³</p> <p>Peer navigation and take-home naloxone for opioid overdose emergency department patients: Preliminary patient outcomes</p> <p>2018</p>	<p>Pilot study of the Lifespan Opioid Overdose Prevention (LOOP) Program.</p> <p>The objective was to examine ED-based OEND with recovery coach consultation and linkage to evidence-based opioid use disorder (OUD) treatment, opioid overdose, and opioid overdose death.</p> <p>ED physicians, per availability and patient/provider discretion, assigned patients to receive one of the following approaches: usual care, THN, or THN and a peer recovery coach consultation.</p>	<p>LOOP was implemented in two EDs in Providence, RI, September 2014-February 2015.</p>	<p>151 of 80,637 ED visits met the inclusion criteria. 39.7% received usual care, 17.2% received THN, 43% received THN and peer recovery coach consultation.</p> <p>28.5% initiated MAT within a year of their ED visit. A shorter, though not statistically significant, median time-to-MAT was observed for those who received a recovery coach consultation (81.5 vs 107 days). 19.9% were treated for repeat overdose within a year of their index visit.</p> <p>4.6% (n=7) died within one year of their index visit. A smaller, though not statistically significant, proportion of deaths occurred among both groups that received naloxone, along with a</p>	<p>No randomization to any treatment arm.</p> <p>Unclear when antagonist-based MAT data are available.</p> <p>Lack of access to recovery coach client records limited evaluation of recovery coach navigation and engagement (dose).</p> <p>ED utilization for repeat overdoses missing for those seen in other hospitals.</p>	<p><i>ED peer recovery consultation and naloxone administration may be effective interventions to decrease time to initiation of medication for OUD and reduce mortality among ED patients treated after opioid overdose.</i></p>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
			longer median time to death.		
Tobin et al.⁵² Evaluation of the Staying Alive programme: Training injection drug users to properly administer naloxone and save lives 2009	Pre-post surveys of OEND program participants	People who inject drugs participating in the "Staying Alive" OEND program, Baltimore, MD, October 2004-April 2005. The program was implemented as a compliment to the Baltimore City Health Department Needle Exchange.	43 of 85 participants had overdose experience before and after OEND training. None had used naloxone during the most recent overdose prior to training compared to 19 (44%) uses during the most recent overdose at 6 months after training. EMS calls declined from 28 reports to 21 (65% to 49%), commonly attributed to regained consciousness. Post-training, majorities of participants endorsed treating overdose themselves with naloxone.	Unclear convenience sample approach to evaluation enrollment (specific sites and times were enrolled) precluded estimation of demand and participation rates. Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. Design limited study sample to 85 of 250 total participants enrolled at baseline.	<i>Our study provides additional evidence to support overdose prevention programs as effective in improving knowledge specific to naloxone use and in training active injection drug users to save lives with naloxone.</i>
Wagner et al.⁵³ Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los	Follow-up surveys of OEND participants.	People who inject drugs participating in an OEND program within a homeless service organization, Los Angeles, CA, September 2006-January 2008	47 of 66 participants who completed OEND training also completed 3-month follow-up (71%). These participants reported statistically significant increases in overall knowledge of 9 overdose risk factor and response items. 19 (40%) reported	Reports of overdoses and reversals are subject to recall bias; under-reporting of naloxone use also possible. Small sample size, unclear whether findings are generalizable to other regions.	<i>This study contributes to a growing literature suggesting that overdose prevention and response training programs for IDUs may be associated with changes in knowledge and overdose response behavior; with few negative</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
Angeles, CA 2010			<p>training a peer in overdose response, and 25 (53%) reported a decrease in drug use since training.</p> <p>22 participants (47%) reported responding to 35 overdoses. Responders reported calling sternum rub (in 26% of overdoses), emergency services (60%), rescue breathing (66%), administering naloxone (80%), and staying with the victim (85%). They also reported lower prevalence of non-recommended responses, the most common being hitting, slapping or shaking a victim (33%). Among those with prior overdose experience (n=12), this was a statistically significant increase in recommended responses.</p>		<i>consequences and the possibility of unforeseen benefits such as reductions in drug use or increased engagement with drug treatment.</i>
Simulation Studies					
Irvine et al. ⁵⁷	Evaluation of provincial THN efforts	British Colombia, 2012-2016.	22,499 ambulance-attended overdoses	Fentanyl was assumed to affect the rate of	<i>The THN programme substantially reduced the</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
Distribution of take-home opioid antagonist kits during a synthetic opioid epidemic in British Columbia, Canada: a modelling study 2018	using a Bayesian framework and Markov chain model.		<p>occurred during the study period, along with 2,121 illicit drug-related deaths and 19,074 THN kits distributed.</p> <p>298 deaths (95% Credible Interval: 91-474) were estimated to have been averted due to THN, with the majority (226) occurring in 2016. The number needed to treat was estimated at 85.2 kits per death averted (95% CrI: 61.1-132.5).</p>	<p>overdose rather than probability of death following overdose.</p> <p>The model was tailored to British Columbia by focusing on increasing fentanyl concentrations in the general drug supply, rather than evolving demographics among PWUD.</p> <p>Unclear effect model input and assumptions; results will be systematically biased with inappropriate model.</p> <p>Has not yet been validated by real-world observational work.</p>	<i>number of overdose deaths during a period of rapid increase in the number of illicit drug overdoses due to fentanyl in British Columbia. [...] Our findings show the value of a fast and effective response at the start of a synthetic opioid epidemic. We also believe that multiple interventions are needed to achieve an optimal impact.</i>
Keane et al.⁵⁶ Effects of naloxone distribution to likely bystanders: Results of an agent-based model 2018	An agent-based model of community-based OEND informed via a sequential exploratory mixed methods design using qualitative data.	Qualitative data were drawn from interviews with substance use treatment providers (n=7) and people at high risk for opioid overdose (n=22), southwestern Pennsylvania, mid-2016.	Compared to a baseline of 335.8 opioid overdose deaths annually, a single, single-kit-distributing OEND program reduced deaths 6.0%, while a lone OEND site distributing 10 kits per visit reduced deaths 8.3%.	<p>Models assumed that a single dose of naloxone was sufficient for a successful reversal. Data were based on a period prior to widespread availability of illicit fentanyl.</p> <p>The agent-based model</p>	<i>Our research indicates the need to increase support for naloxone distribution via harm reduction sites, such as syringe exchange programs, since these sites are more likely to engage people at high risk for overdose deaths,</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
			<p>Adding secondary social network exchange of naloxone to the model reduced deaths 42.5% with a single OEND site. The effect of 10 sites distributing 10 kits per visit without social network exchange was a 39.9% decrease. When combining multi-kit distribution with social network distribution and multiple OEND sites, deaths decreased 61.1%. Adding distribution through a needle exchange site reduced death 65%.</p>	<p>based on a theoretical city and has limited generalizability. Certain behaviors related to harm reduction are not well-studied and had to be estimated in the absence of empirical data.</p> <p>Simulations of only people at high risk of overdose were conducted.</p> <p>Unclear effect model input and assumptions; results will be systematically biased with inappropriate model.</p> <p>Has not yet been validated by real-world observational work.</p>	<i>that is, people who use opioids.</i>
Pitt et al.⁵⁵ Modeling Health Benefits and Harms of Public Policy Responses to the US Opioid Epidemic	<p>Dynamic compartmental modeling of pain, opioid use, and opioid addiction health states.</p> <p>11 interventions were assessed, including:</p>	General US adult population, projected from 2016 to 2025.	Over a 5-year period, increasing naloxone availability, needle exchange, MAT, and psychosocial treatment increased life years and quality-adjusted life years (QALYs) and reduced	Forecasts based on current opioid overdose data, but many other assumptions need to be made in the absence of empirical data, like estimating the number transitioning to heroin,	<i>Our results suggest that some policy responses to the opioid epidemic may reduce prescription opioid misuse but increase heroin use, blunting or even eliminating any public</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
2018	acute, transitioning to chronic, and chronic prescribing of opioids; drug rescheduling; PDMP use; reformulation of drugs; unused opioid disposal; naloxone availability; needle exchange; MAT; and psychosocial treatment.		deaths. No single policy was likely to reduce deaths over a 5 or 10-year period. However, increasing naloxone availability resulted in the greatest reduction in deaths among all intervention studied over 5 years (4.3%), and 10 years (4.1%).	and quantifying the potential policy effects. Unclear effect model input and assumptions; results will be systematically biased with inappropriate model. Has not yet been validated by real-world observational work.	<i>health benefit in the short term (e.g., the next 5 years) but yielding net positive health benefits in the longer term.</i>
Uyei et al. ⁵⁸ Effects of naloxone distribution alone or in combination with addiction treatment with or without pre-exposure prophylaxis for HIV prevention in people who inject drugs: a cost-effectiveness modelling study 2017	Cost-effectiveness evaluation of four harm reduction and treatment interventions using a simulation model. The interventions evaluated included OEND, OEND plus treatment linkage, OEND plus pre-exposure prophylaxis (PrEP) for HIV, and OEND with treatment linkage and PrEP, compared to each other and no intervention.	A decision analytical Markov model of opioid overdose, HIV incidence, overdose-related deaths, and HIV-related deaths among PWID in Connecticut. Model parameters were based on empirical, published data.	The incremental cost-effectiveness ratio (ICER) for OEND was \$323 per QALY. The most efficient strategy overall was OEND plus treatment linkage. However, at a willingness-to-pay threshold of \$100k per QALY, OEND with linkage and PrEP was most effective, with an ICER of \$95,337 and better outcomes compared to OEND with treatment linkage only.	Hepatitis C and other downstream effects (including incarceration) were not simulated. Unclear effect model input and assumptions; results will be systematically biased with inappropriate model. Has not yet been validated by real-world observational work.	<i>Our analyses suggest that naloxone distribution through syringe service programmes provides good value for money compared with no additional intervention. The addition of linkage to addiction treatment saves money compared with either no additional intervention or naloxone distribution alone. Combining PrEP with naloxone distribution and linkage to addiction treatment resulted in the greatest health gains and was</i>

Author, title, year	Study design	Population/setting	Summary of results	Limitations	Authors' conclusion
			The authors' note that while possible moral hazard of naloxone was not considered, sensitivity analyses conducted with increased overdose rates did not change findings.		<i>cost-effective, with an ICER of less than \$100,000 per QALY gained.</i>

Estimates of the Annual Health System Costs of Naloxone Co-Prescribing

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Executive Summary

Naloxone co-prescribing may contribute to increases in health system spending depending on how many patients are affected.

In this analysis, we develop an economic model to estimate the potential health system costs of naloxone co-prescribing, assuming that all of the need is met through community-use naloxone products (i.e. approved auto-injectors and nasal sprays).

We find that co-prescribing naloxone to all patients who are dispensed an opioid analgesic prescription could increase health system costs by \$63.9 billion to \$580.8 billion per year. Focusing on smaller patient populations could substantially diminish these costs, but in most cases there is still the potential for annual costs exceeding \$1 billion.

Given the potential costs identified in our analysis, it is important that patient populations are targeted that would most benefit from increased naloxone availability without burdening the health system.

Introduction

Naloxone co-prescribing may contribute to increases in health system spending depending on how many patients are affected. Initially, more patients could receive and fill prescriptions for the drug while prices are already above historical levels. ¹ As time goes by, increases in demand for naloxone could contribute to further price increases, particularly if manufacturers have limited production capacity.

In this analysis, we develop an economic model to estimate the potential health system costs of naloxone co-prescribing, assuming that all of the need is met through community-use naloxone products (i.e. FDA-approved auto-injectors and nasal sprays). We consider multiple populations, starting from all patients receiving an opioid analgesic prescription and ending with narrower groups that have been targeted by guidelines recently issued by the Surgeon General. ² To our knowledge, this is the first quantitative evaluation of the potential impacts of this policy.

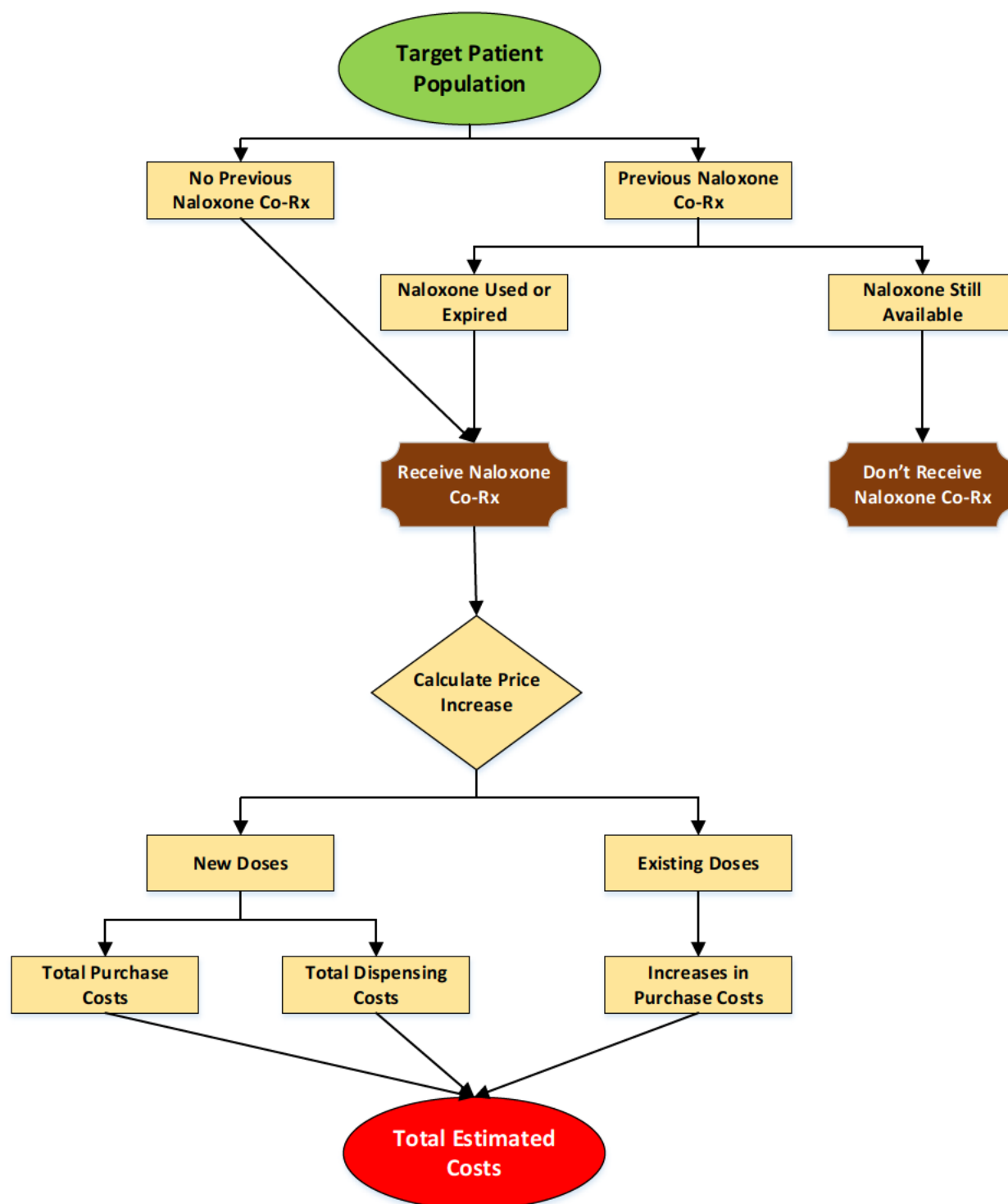
We believe that these results can aid policymakers and other stakeholders as they decide whether to implement naloxone co-prescribing and how broadly. Given the potential costs identified in our analysis, it is important that patient populations are targeted that would most benefit from increased naloxone availability without unreasonably burdening the health system.

Methods

We develop an economic model to estimate additional health system costs from naloxone co-prescribing based on published and proprietary information sources. We assume that co-prescribing needs will be met by community-use naloxone products, which we define as FDA-approved auto-injectors and nasal sprays. We apply our model to populations identified by recent Surgeon General guidelines since we believe that these are potential candidates for implementing this policy. ²

Figure 1 provides an overall summary of our economic model.

Figure 1 – Overview of the Naloxone Co-Prescribing Economic Model



We develop our cost estimates in three phases (see our Technical Appendix for more detailed information about our approach and assumptions). First, we estimate how

many new doses of naloxone will be needed on average for a patient population of a given size once the policy is fully implemented (i.e., when most opioid analgesic users in that population prescribed for chronic pain have received their initial co-prescription). We divide these potential patients into two groups: those who have never or not recently received a naloxone co-prescription, and those who have received one at some point in the recent past (e.g., within the last 2 years). The former set of individuals are always co-prescribed naloxone, while the latter ones only receive a co-prescription if they've either used up their previous prescription to reverse overdose(s) or their doses have expired. Those patients who receive a naloxone co-prescription can choose either to fill it or not, and if they do fill it they receive two doses of a community-use naloxone product.

We then use a constant elasticity supply and demand model to estimate how much this change in demand might increase the price of community-use naloxone products. We calculate the fractional change in demand by dividing the previous number by the total number of community-use naloxone doses dispensed in retail pharmacies during calendar year 2017. We then scale the resulting price to account for two scenarios: (1) *With Generics*, which assumes that higher prices for community-use naloxone products attract many generic competitors into the market; (2) *Without Generics*, which assumes that the status quo continues in this market due to entry barriers such as patents and exclusivities.

Finally, we use these results to estimate overall increases in health system spending. We combine two types of health system costs that could stem from naloxone co-prescribing. One of these is costs accrued from newly prescribed doses, including for each dose its total purchase price and dispensing costs. The other is additional spending due to price increases for doses that were already in use.

Results

We divide the included patient populations (see Table A2 in our Technical Appendix for more information on how these are defined) into two main groups.

Table 1 provides cost estimates for populations that we believe more frequently interact with the health system and are more likely to be affected by naloxone co-prescribing. We estimate that co-prescribing naloxone to all patients who are dispensed an opioid analgesic prescription would increase costs to the health system by \$63.9 billion to \$580.8 billion per year. Our estimates suggest that reducing the number of included patients could substantially reduce the costs, but in all cases except for one the potential still exists for costs exceeding \$1 billion per year.

Table 1 – Estimated Costs of Naloxone Co-Prescribing with Community-Use Products for Populations that More Frequently Interact with the Health System

Population	# Patients (Millions)	Annual Cost w/ Generics (\$ Billions)	Annual Cost w/o Generics (\$ Billions)
All Opioid Analgesic Rx	58.0	63.9	580.8
High-Impact Chronic Pain	19.6	9.5	96.1
Rx Opioid Analgesics with CNS Depressants	3.5	0.6	5.4
Medication Assisted Treatment (MAT)	1.4	0.2	1.5
Opioid-Related ED Visit	0.8	0.1	0.8

Table 2 provides cost estimates for populations that we believe less frequently interact with the health system and which may be more difficult to reach with this intervention. These results largely mirror those in Table 1, except for approaches that target patients with a recent criminal justice interaction; these patient populations are estimated to contribute costs of less than \$1 billion per year.

Table 2 – Estimated Costs of Naloxone Co-Prescribing with Community-Use Products for Populations that Less Frequently Interact with the Health System

Population	# Patients (Millions)	Annual Cost w/ Generics (\$ Billions)	Annual Cost w/o Generics (\$ Billions)
Misusing Opioids	11.4	3.8	34.3
Opioid Use Disorder	2.1	0.3	2.6
Recent Criminal Justice and Rx Opioid Misuse	0.9	0.1	0.8
Recent Criminal Justice and Heroin Use	0.4	0.0	0.3
Recent Criminal Justice and Opioid Use Disorder	0.3	0.0	0.2

Discussion

Our economic model suggests that the annual costs of implementing naloxone co-prescribing with community-use naloxone products could be as high as tens to hundreds of billions of dollars. These costs could be reduced by either focusing on a targeted group of at-risk patients or through more competition from generic versions of these products.

We are uncertain about how long it might take for community-use naloxone products to become eligible for generic approvals. These naloxone products consist of drug-device combinations that are covered by numerous patents identified in FDA’s *Orange Book*, some of which do not expire until 2035.³ While it is possible that higher revenues for

community-use naloxone products could encourage aggressive patent challenges, it appears possible that initial costs may be towards the higher end of our estimates.

For some patient populations, particularly if there is little to no generic competition, implementing co-prescribing could make naloxone the largest pharmaceutical market by revenue. According to IQVIA, the highest selling drug in calendar year 2017 by dollar value was Humira (adalimumab), with sales of \$16.9 billion. ⁴

If naloxone co-prescribing is targeted at all patients who are dispensed an opioid analgesic prescription, annual costs could potentially exceed total US spending for pharmaceuticals, which IQVIA estimated at \$452.6 billion in calendar year 2017. ⁴ Furthermore, costs for this group could also exceed the overall economic costs of the opioid crisis, which the Council of Economic Advisers (CEA) recently estimated were \$504.0 billion in calendar year 2015. ⁵

It is important to note that our economic model is subject to several limitations that contribute additional uncertainty about the costs of naloxone co-prescribing. First, our model relies on numerous assumptions from published literature and proprietary data sources, each of which has its own uncertainties and limitations. Second, our supply and demand model may underestimate potential price increases if manufacturers lack spare production capacity to ramp up and meet the needs of these patient populations. Finally, our model assumes that all eligible patients receive a naloxone co-prescription, which may potentially overestimate the actual costs depending on how strictly healthcare providers follow labeling or other guidelines and the extent to which naloxone prescriptions are filled.

Conclusions

Naloxone co-prescribing could contribute to potentially large increases in health system spending depending on how broadly it is implemented. Therefore, it would be important that any naloxone co-prescribing policy be targeted – to the extent possible – at patients who would most benefit from increased naloxone availability without unreasonably burdening the health system.

Further research is needed to better understand the potential benefits of naloxone co-prescribing, such as reduced deaths and improved quality of life from more quickly rescuing patients. Information that might inform this discussion could include overdose rates within different patient groups, how much broader access to naloxone could reduce the time it takes to administer naloxone, and how eventual health outcomes vary with the amount of time it takes to reverse an overdose.

Technical Appendix

This technical appendix provides more detailed information about the approach and assumptions that underpin our economic model as a supplement to the Methods and Results sections.

Table A1 includes a complete listing of the assumptions that will be described in further detail below.

Table A1 – Assumptions Used in the Naloxone Co-Prescribing Economic Model

Assumption	Abbreviation	Value	Source	Notes
Number of Co-Rx Eligible Patients	N_{Patients}	Varies	Varies	See Table A2
Fraction of Patients with Recent Naloxone Co-Rx	$\text{Frac}_{\text{Recent}}$	96.6%	2017 NSDUH, ⁶ IQVIA TPT ⁷	1-(Rx Pain Reliever Initiations/ $N_{\text{Rx Users}}$). This excludes patients who haven't received a naloxone co-Rx in several years.
Fraction of Naloxone Doses Used Per Year	$\text{Frac}_{\text{Used}}$	5.7%	Wheeler et. Al, 2015 ⁸	Overdose Reversals/Vials Distributed in CY 2013
Shelf Life of Naloxone	Shelf	21 Months	NCHRC ⁹	Midpoint of the 18-24 month range
Rate of Written Prescriptions Filled	$\text{Frac}_{\text{Adhere}}$	70%	Abrams et al., 2017 ¹⁰	Based on the rate for Epinephrine Auto-Injector in Canada
Total Number of Patients Receiving an Rx Opioid	$N_{\text{Rx Users}}$	58 million	IQVIA TPT ⁷	Defined as an opioid analgesic in CY 2017
Total Number of Dispensed Community-Use Naloxone Doses	Doses_{Rx}	1,033,466	IQVIA NPA ¹¹	Two times total Rx dispensed in retail pharmacies in CY 2017
Price Elasticity of Supply for Community-Use Naloxone	ϵ_S	1	FDA Assumption	We were unable to find a value in the published literature for pharmaceuticals, so we assume a linear supply curve. We believe this underestimates costs by ignoring short- to medium-run capacity limits.
Price Elasticity of Demand for Community-Use Naloxone	ϵ_D	-0.21	Gemmil, 2007 ¹²	Demand elasticity is for all pharmaceuticals
Average Retail Price of Community-Use Naloxone	N/A	\$478.41	IQVIA NPA ¹¹	Average exit pharmacy price for CY 2017, weighted by number of doses
Production Cost as a Percentage of Retail Price	N/A	11%	FDA Unpublished Analysis ¹³	Estimated median price differential for generic drugs with 8 competitors, relative to the average price over the 6 months prior to initial generic entry. We derive this estimate using IQVIA NSP data from 2012-2017, and adjust for inflation using the CPI-U.
Prescription Fill Cost	N/A	\$7.88	CCPA, 2015 ¹⁴	Counts payroll and prescription department costs. Adjusted to December 2017 dollars using the CPI-U.

We begin our model by estimating how many additional doses of community-use naloxone on average will be required to meet the needs of a particular patient population. We first estimate the total number of doses separately for patients who have recently and not recently received a naloxone co-prescription according to formulas (1) and (2) respectively.

For patients with recent co-prescriptions, we argue that their doses need to be replaced only if they have been used to reverse overdose(s) or have expired (if not used). We assume that expired doses turn over at a constant rate, i.e. that they have a fixed shelf life and were originally allocated uniformly across time.

For patients without recent co-prescriptions, we assume that they will always be co-prescribed a community-use naloxone product.

In both cases, patients can choose whether or not to adhere to filling their prescription, and if they fill their prescription they receive two doses (i.e. two auto-injectors or two nasal sprays).

$$(1) \text{Doses}_{\text{Recent}} = N_{\text{Patients}} \times \text{Frac}_{\text{Recent}} \times \left(\text{Frac}_{\text{Used}} + (1 - \text{Frac}_{\text{Used}}) \times \left(\frac{12}{\text{Shelf}} \right) \right) \times \text{Frac}_{\text{Adhere}} \times 2$$

$$(2) \text{Doses}_{\text{Not Recent}} = N_{\text{Patients}} \times (1 - \text{Frac}_{\text{Recent}}) \times \text{Frac}_{\text{Adhere}} \times 2$$

We then estimate the number of existing doses for that patient population according to formula (3). We assume that doses have previously been dispensed proportionally to the size of a patient population.

$$(3) \text{Doses}_{\text{Existing}} = \frac{N_{\text{Patients}}}{N_{\text{Rx Users}}} \times \text{Doses}_{\text{Rx}}$$

Finally, we calculate the additional number of naloxone doses using formula (4).

$$(4) \text{Doses}_{\text{Additional}} = \text{Doses}_{\text{Recent}} + \text{Doses}_{\text{Not Recent}} - \text{Doses}_{\text{Existing}}$$

With this number in hand, we develop a constant elasticity supply and demand model to estimate how much the increase in demand would increase the price of community-use

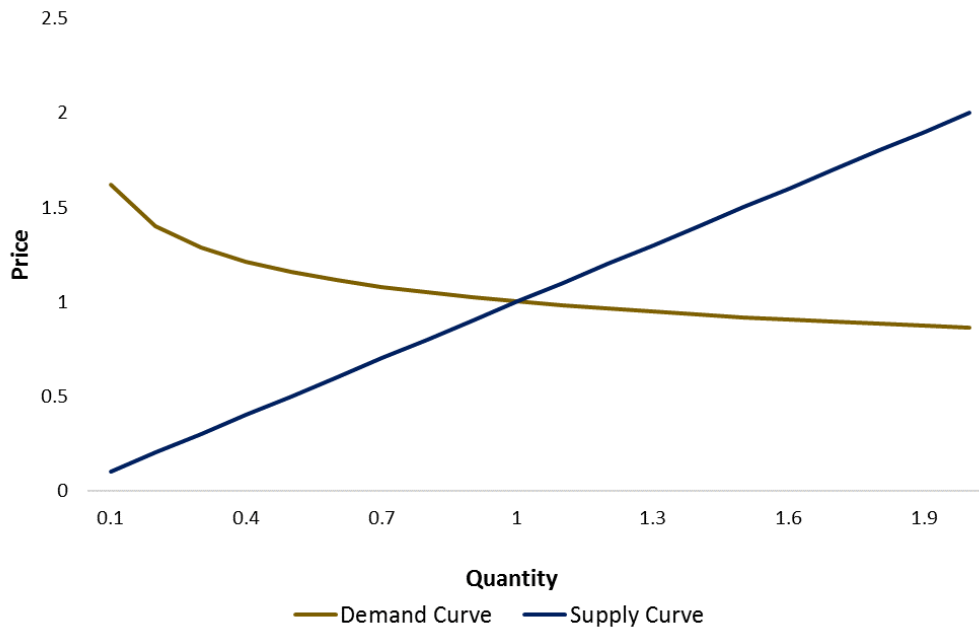
naloxone products. This model, while a simplification of the naloxone market,^a has the advantage that it relies on just two key assumptions – the supply and demand elasticities – which are more readily available in the published literature.

Formulas (5) and (6) describe the supply and demand curves respectively within this framework, where Q and P correspond to quantity and price respectively, and A is a scaling factor. Figure A1 also provides a graphical representation of these supply and demand curves with A set equal to 1, and the two elasticities equal to 1 and -0.21 respectively (equivalent to our assumptions).

$$(5) Q_S = A_S P^{\epsilon_S}; \epsilon_S \geq 0$$

$$(6) Q_D = A_D P^{\epsilon_D}; \epsilon_D \leq 0$$

Figure A1 – Example of a Constant Elasticity Supply and Demand Model



Using (5) and (6), we calculate the fractional price change (P'/P) in formula (7) in terms of the fractional change in demand (A'_D/A_D), where the latter quantity is estimated according to formula (8).

^a One disadvantage of this model is that it becomes less reliable for large shifts in demand by assuming that patients are similarly price inflexible even when prices have risen by thousands of percent

$$(7) \frac{P'}{P} = \frac{A'_D}{A_D}^{\left(\frac{1}{\epsilon_s - \epsilon_D}\right)}$$

$$(8) \frac{A'_D}{A_D} = \frac{\text{Doses}_{\text{Additional}} + \text{Doses}_{\text{Rx}}}{\text{Doses}_{\text{Rx}}}$$

We apply this fractional change to production cost and retail price respectively to define our *With Generics* and *Without Generics* scenarios. We estimate the retail price of community-use naloxone using the average exit pharmacy price of community-use naloxone doses dispensed in calendar year 2017, weighted by prescription volume, based on data from the IQVIA National Prescription Audit (NPA). We estimate production cost by multiplying the retail price by 11%, which an unpublished FDA analysis, using data from the IQVIA National Sales Perspective (NSP), estimated is the median decline in price for generic drugs with 8 competitors.

Finally, we estimate total costs separately for additional and existing naloxone doses. For the former, we apply the entire purchase price to this number as well as a \$7.88 fill cost per prescription (i.e. per every 2 doses). For the latter, we multiply (3) by the absolute change in price, i.e. $P' - P$. We then add up these two figures to obtain our final estimate of the total cost of naloxone co-prescribing.

We apply this model to each of the patient populations defined below in Table A2.

Table A2 – Patient Populations Used for the Naloxone Co-Prescribing Cost Estimates

Population	# Patients (Millions)	Description	Source
All Opioid Analgesic Rx	58.0	National estimates of patients with opioid analgesic prescriptions from retail pharmacies	IQVIA TPT ⁷
High-Impact Chronic Pain	19.6	Patients with chronic pain limiting life or work activities on most days or every day within the last 6 months	Dahlhamer et al, 2018 ¹⁵
Misusing Opioids	11.4	Misuse or abuse, per the NSDUH definition	2017 NSDUH ⁶
Rx Opioid Analgesics with CNS Depressants	3.5	Concomitant use of Rx opioids with CNS depressants (benzodiazepines and sleep aids) in Medicare Part D enrollees	CMS, 2016 ¹⁶
Opioid Use Disorder	2.1	Per the NSDUH definition	2017 NSDUH ⁶
Medication Assisted Treatment (MAT)	1.4	Patients receiving methadone (SAMHSA), buprenorphine MAT (IQVIA), or extended-release naltrexone (SAMHSA). May include some overlap between the groups.	IQVIA TPT ⁷ ; 2015 N-SSATS ¹⁷
Recent Criminal Justice and Rx Opioid Misuse	0.9	Any arrest, parole, or probation in the past 12 months, with prescription opioid misuse per the NSDUH definition	Winkelman et al., 2018 ¹⁸
Opioid-Related ED Visit	0.8	Any type of visit driven by acute conditions related to opioid use, excluding GI-related visits. Estimated by taking the rate (243.5 per 100,000 in 2016) and extrapolating it to the US Population (329 million).	HCUP, 2015 ¹⁹ ; US Census Bureau ²⁰
Recent Criminal Justice and Heroin Use	0.4	Any arrest, parole, or probation in the past 12 months, with reported heroin use, per the NSDUH definition	Winkelman et al., 2018 ¹⁸
Recent Criminal Justice and Opioid Use Disorder	0.3	Any arrest, parole, or probation in the past 12 months, with reported opioid use disorder, per the NSDUH definition	Winkelman et al., 2018 ¹⁸

Database Descriptions

IQVIA National Prescription Audit™(NPA)¹¹

The IQVIA National Prescription Audit (NPA) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 58,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

IQVIA Total Patient Tracker™ (TPT)⁷

IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of ~58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies.

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U.S. FOOD & DRUG
ADMINISTRATION

Memorandum

To: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

From: Barbara R. Cohen, MPA
Social Science Analyst
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Office of New Drugs
CDER, FDA

Date: November 19, 2018

Subject: December 17-18, 2018, AADPAC/DSaRM meeting to discuss strategies to increase the availability of naloxone products intended for use in the community

Nonprescription Model Drug Facts Label Project

Naloxone is a prescription drug. One possible means of expanding access to naloxone would be through nonprescription availability. The Division of Anesthesia, Analgesia, and Addiction Products requested that the Division of Nonprescription Drug Products (DNPD) provide a brief document describing how OTC consumer development programs work, and information on a project that DNPD has implemented - the Nonprescription Model Drug Facts Label Project. This project is intended to facilitate a potential nonprescription naloxone development program.

Project Background: OTC Consumer Development Programs

In order to obtain approval for a nonprescription drug, Sponsors typically need to develop a draft Drug Facts Label (DFL) and then conduct consumer behavior studies to demonstrate that consumers can safely and effectively use the drug utilizing the DFL without any other training or healthcare provider assistance. Consumer behavior studies requested by FDA can range from label comprehension studies to human factors to self-selection to actual use studies, depending on the nature of FDA reviewers' clinical concerns about potential consumer use. Label comprehension studies assess whether consumers can understand the key label messages. Self-selection studies examine whether consumers understand from the label whether or not the product is appropriate for them personally to use, given the labeled warnings and instructions to ask a doctor or pharmacist before use. Human factors studies focus on the risk associated with observed use errors, such as with a drug administered through a device. Actual use studies determine whether consumers can use the product on their own in accordance with labeled directions.

FDA had discussed OTC consumer development programs with industry stakeholders at a July 2015 scientific workshop on Exploring Naloxone Uptake and Use, held in collaboration with the National Institutes of Drug Abuse, the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, and the Health Resources and Services Administration. The feedback subsequently received from potential Sponsors was that they perceived the need to do these studies as a barrier to development of a nonprescription naloxone product. This concern led FDA officials to initiate the Nonprescription Model Drug Facts Label Project.

Project Rationale

In 2016, FDA implemented a novel initiative as part of its efforts to combat the growing epidemic of opioid overdose deaths. The Nonprescription Model Drug Facts Label Project was launched with the goal of expanding naloxone availability by aiding Sponsors who wish to pursue development of a nonprescription form of naloxone. Availability of nonprescription naloxone could make it broadly available on store shelves for purchase by consumers, without the mandatory involvement of a health care intermediary or EMS responder. Although the availability of naloxone had already been significantly expanded by states and communities through programs using standing prescriptions, those state programs still require interaction with a healthcare professional, and this initiative sought to take access a step further – with the eventual goal of enabling anyone to go to a store to obtain naloxone without encountering real or significant perceived barriers to doing so. This would help further facilitate the vision subsequently articulated in April 2018 by the U.S. Surgeon General. In his advisory on Naloxone and Opioid Overdose – the first Surgeon General Advisory in ten years, he stated:

“We are in the middle of an opioid epidemic that claims 115 lives each day – or one person every 12.5 minutes...I am urging more individuals, especially family, friends, and those who are personally at risk for an opioid overdose, to keep naloxone on hand...it is not a long term solution, but it can temporarily suspend the effects of the overdose until emergency responders arrive. Each time naloxone is delivered, it is a potential turning point for the individual who may be struggling with opioid use.”

To facilitate OTC naloxone availability, the Nonprescription Model Drug Facts Label Project embodied an innovative approach – FDA itself would design a model DFL and then iteratively refine and evaluate consumer comprehension of the label through a contract with an experienced consumer behavior research firm. After completion of the study report, if the study is determined to be successful from an independent FDA review of the data, the resulting DFL could be utilized by any Sponsor as an already approved template. After consideration of multiple factors, such as the circumstances of use, and the practicality of study conduct, FDA believes that label comprehension is the key consumer behavior study type to be conducted, and that self-selection and actual use studies are likely not needed. Using the model DFL template, a Sponsor could add information specific to their particular device to the DFL, and then assess through human factors the specifics of their particular product’s use. If the label comprehension study is not successful, it could still provide valuable information to potential Sponsors about what worked and what did not.

FDA’s Development of Initial DFL

FDA faced a significant challenge in reducing the Rx Full Prescribing Information and patient instructions down to the key essentials for a DFL. Sponsors typically face these challenges, but this was particularly unique in that naloxone is intended to be administered by one person to another, in a situation where one person is unresponsive and every second counts. Furthermore, the person administering the product also needs to call

911 and stay with the unresponsive person to prevent death by relapse, as well as to continue to dose at 2-3 minute intervals if the person is not revived – all in a highly stressful situation in which s/he may be reading the DFL for the very first time. In light of these unprecedented circumstances, FDA made the deliberate decision to significantly simplify the DFL by distilling it to its key elements. The Agency solicited input from the addiction treatment community, including naloxone distribution programs, as well as both internal and external substance abuse experts, in order to identify recurring themes and best practices. This information was synthesized to determine the key elements for inclusion in the DFL.

Input was also sought from internal communications experts about the best ways to present the desired information on a DFL. The resulting DFL was accompanied by adjacent pictograms – a first for nonprescription DFLs. As two product forms of naloxone were available at the time the study was initiated (nasal spray and auto-injector), proposed model labels were developed for each. The labels were identical except for a placeholder section that described administration. The two different DFLs would be assessed by being rotated alternatively during the study.

Research Contract for Label Comprehension Study

Simultaneous to model DFL development, FDA crafted a Statement of Work (SOW) that was based upon the fundamental principles outlined in the guidance for industry: *Nonprescription Label Comprehension Studies*. Key among these were that the study population should: 1) include all subjects who could potentially use nonprescription naloxone; 2) include an adequate number of subjects with limited literacy skills and 3) be large enough to provide a reliable demonstration of key communication objectives. The SOW also incorporated best practices in the form of three study tasks: 1) iterative design allowing for the DFL to evolve in real time as qualitative feedback was gathered from participants in unstructured cognitive interviews, 2) a pilot study to evaluate the evolving DFL as well as recruitment methods, interviewing methods, data collection tools, and appropriate sample size for the pivotal study and 3) a pivotal quantitative study.

Regarding the study population, FDA specified in the SOW that adult prescription opioid users, family and friends of prescription opioid users, adult heroin users, and family and friends of heroin users, be recruited for study participation in various geographic areas throughout the United States. Additionally, FDA also stated that adolescent and adult “all-comers”, that is, participants recruited through various research sites throughout the United States, should be included. FDA moreover directed that the study population be comprised of approximately 33% limited literacy participants, reflecting national estimates of the prevalence of limited literacy.

A competitive award process was utilized to award the research contract. The contract was awarded to Research Triangle Institute (RTI), a research contractor with significant expertise in community-based research with substance abuse populations. RTI partnered with Concentrics Research, a firm experienced in label comprehension studies in the nonprescription space.

Key Learnings from Tasks 1 and 2

In Task 1, overall, participants demonstrated understanding of the key concepts. During Task 1, the DFL was revised to incorporate more of a “step” approach. The “talk-aloud” exercise asking participants to repeat back the steps demonstrated that most participants could easily follow the five key instructions in the listed sequence: 1) Check if you suspect an overdose; 2) Give the first dose; 3) Call 911; 4) Watch and continue to give

doses if necessary; 5) Stay with the person until the ambulance arrives. Participants had some difficulty locating critical information on the DFL, and there were issues with clarity of some of the pictograms as well as some of the wording used on the label; changes were made to address these observations. In Task 2, the DFL was further refined and the pilot questionnaire assessed and revised to enhance clarity of the scenario-based questions.

Task 3 - Pivotal Label Comprehension Study Design and Conduct

The pivotal study, Task 3, was a multisite single visit label comprehension study. Interested participants underwent minimal screening, either by telephone or online. Those who qualified were invited to a local research site. Upon arrival at the site, each adult participant reviewed and signed a consent form. Adolescent participants were required to provide signed parental permission, and then reviewed and signed an assent form. The Rapid Estimate of Adult Literacy in Medicine (REALM) test was administered to adult participants to classify the participant as normal or limited literacy. The REALM-Teen test was administered to adolescent participants, ages 15-17, to classify the participants as normal or limited literacy. The participant was then provided with the DFL to review, and the interviewer left the room to give the participant the opportunity to read the DFL independently and at his or her own pace. Once the participant indicated that he or she was finished reading the labeling, the interviewer returned to the room. This method is typical for label comprehension studies. (Note: all interviewers completed cultural sensitivity training conducted by RTI experts on the unique challenges and considerations of working with drug users).

Because the DFL has sequential steps outlined, a cognitive walkthrough method was used to allow the participant to talk aloud through the steps. After this process, a structured label comprehension interview was conducted. (This represents an innovative hybrid approach for label comprehension studies, and may have applicability to other products). The label comprehension questions were composed mainly of open ended third party scenario questions; however, there were also direct questions in the questionnaire. These questions required participants to make decisions based on the product uses, warnings, and directions on the DFL. After each label comprehension question, a follow-up question was asked to gain insight into the reason for the participants' response(s) ("Why do you say that"?). Data were analyzed based on the formal Statistical Analysis Plan (SAP) and pre-established coding rules, developed by FDA and the contractor, as well as post hoc guidelines established for unanticipated responses that were not mentioned by participants in Tasks 1 and 2. Responses from the cognitive walkthrough and comprehension interview (initial response and follow-up response) were considered in the analysis to determine a correct or incorrect response. The study design and all study materials for each task were approved by FDA's Research Involving Human Subjects Committee (RIHSC) and RTI's Institutional Review Board (IRB) as well as the Office of Management and Budget.

The study was completed with 710 unique participants in the total analysis population, of which 33.4% (n=237) had limited literacy:

- Group 1-2: Adult opioid users and associates, aged 18 or older: Population of adult prescription opioid users and/or heroin users and/or illicit fentanyl users as well as family/friends who were not users themselves, 18 or older (n=430)
 - N=275 Rx opioid users
 - N=321 Heroin users
 - N=144 Illicit fentanyl users
 - Note: overlapping categories above included in total of n=430

- Group 3: Adolescent all-comers aged 15-17: Population of adolescents intended to represent the general population 15-17 years (n=140)
- Group 4: Adult all-comers aged 18 or older: Population of adults intended to represent the general population 18 years or older (n=140)

Recruitment for prescription opioid and heroin users and associates was conducted from June-August 2018. Participants were recruited through community-based organizations (CBOs), advertisements posted online, and participant referral. The study team partnered with CBOs in Chicago, Illinois; Charleston, West Virginia; San Francisco, California; and Raleigh-Durham/Vance County, North Carolina to recruit participants and conduct data collection onsite. Additional CBOs in each location partnered with the study team to distribute recruitment materials to their clients. Recruitment for adolescent all-comers was conducted beginning in May 2018 in Tampa, Florida; Dallas, Texas; Los Angeles, California; Indianapolis, Indiana; Raleigh, North Carolina; and New York, New York. Marketing research firm recruitment staff identified potential participants through their community partners and/or proprietary databases. Recruitment of adult all-comers was conducted from May-June 2018 in the same sites as the adolescent all-comers.

Primary endpoints were as follows, with prespecified lower bound thresholds:

- Check for suspected overdose (85%)
- Give the first dose (85%)
- Call 911 immediately (90%)
- Repeat doses every few minutes until fully awake or until emergency personnel arrive (85%)
- Stay with the person until the ambulance arrives (85%)
- Product use: for the treatment of opioid overdose (80%)
- Signs of overdose – if you think someone used an opioid, and the person woke up or is not breathing well, these are signs of an overdose (80%)
- Check for suspected overdose AND give the first dose of this medicine AND call 911 immediately (composite endpoint) (85%)

Secondary endpoints were as follows (no thresholds):

- It is safe to keep giving doses
- Give another dose if the person becomes very sleepy again
- Call 911 after checking and administering the first dose
- Some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry
- Correct mention of steps 1-5 order in the DFL.

Current Status of Study

The study is complete and, as of the time of writing of this briefing document, the study report is undergoing review by an independent team of FDA reviewers. Once the review is finished, the results will be released publicly.

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

2 mg

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 in adults and pediatric patients. (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)
- Administer additional doses of EVZIO, using a new auto-injector, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses of EVZIO 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)
- 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: 2 mg/0.4 mL naloxone hydrochloride solution in a pre-filled auto-injector. (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 the patient under continued surveillance and administer repeated doses of naloxone using a new EVZIO, as necessary, while awaiting emergency medical assistance. (5.1)
- **Risk of Limited Efficacy with in 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 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 most commonly observed in EVZIO clinical studies: dizziness and injection site erythema. (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: 10/2016

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FULL PRESCRIBING INFORMATION

1 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 in adults and pediatric patients.

EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present.

EVZIO is not a substitute for emergency medical care.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

EVZIO is for intramuscular and subcutaneous use only.

Because treatment of suspected opioid overdose must be performed by someone other than the patient, instruct the prescription recipient to inform those around them about the presence of EVZIO and the *Instructions for Use*.

Instruct the patient or caregiver to read the *Instructions for Use* at the time they receive a prescription for EVZIO. Emphasize the following instructions to the patient or caregiver:

- Seek emergency medical care immediately after use. Since the duration of action of most opioids exceeds that of naloxone hydrochloride and the suspected opioid overdose may occur outside of supervised medical settings, seek immediate emergency medical assistance, keep the patient under continued surveillance until emergency personnel arrive, and administer repeated doses of EVZIO as necessary. Always seek emergency medical assistance in the event of a suspected, potentially life-threatening opioid emergency after administration of the first dose of EVZIO.
- Additional doses of EVZIO may be required until emergency medical assistance becomes available.
- Do not attempt to reuse EVZIO. Each EVZIO contains a single dose of naloxone.
- Visually inspect EVZIO through the viewing window for particulate matter and discoloration prior to administration. Do not administer unless the solution is clear and the glass container is undamaged.
- EVZIO must be administered according to the printed instructions on the device label or the electronic voice instructions (EVZIO contains a speaker that provides voice instructions to guide the user through each step of the injection). **If the EVZIO 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 its label.**
- Once the red safety guard is removed, EVZIO must be used immediately or disposed of properly. Do not attempt to replace the red safety guard once it is removed.

Upon actuation, EVZIO automatically inserts the needle intramuscularly or subcutaneously, delivers the naloxone hydrochloride injection, and retracts the needle fully into its housing. Post injection, the black base locks in place, a red indicator appears in the viewing window, and electronic visual and audible instructions

signal that EVZIO has delivered the intended dose of naloxone hydrochloride and instructs the user to seek emergency medical attention.

2.2 Dosing Information

Initial Dosing

Administer the initial dose of EVZIO to adult or pediatric patients intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary, and seek emergency medical assistance. Administer EVZIO as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death.

Repeat Dosing

The requirement for repeat doses of EVZIO depends upon the amount, type, and route of administration of the opioid being antagonized.

If the desired response is not obtained after 2 or 3 minutes, an additional dose of EVZIO may be administered. If there is still no response and additional doses are available, additional doses of EVZIO may be administered every 2 to 3 minutes until emergency medical assistance arrives. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

If the patient responds to EVZIO and relapses back into respiratory depression before emergency assistance arrives, an additional dose of EVZIO may be administered.

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and may require higher doses of naloxone hydrochloride or repeated administration of EVZIO.

Dosing in Adults and Pediatric Patients over Age One Year

Instruct patients or their caregivers to administer EVZIO according to the *Instructions for Use*, intramuscularly or subcutaneously.

Dosing in Pediatric Patients under Age One Year

In pediatric patients under the age of one year, the caregiver should pinch the thigh muscle while administering EVZIO. Carefully observe the administration site for signs of infection following injection and resolution of the opioid emergency.

There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. In these settings, consider use of an alternative, naloxone product which can be titrated to effect and, where applicable, dosed according to weight [*see Use in Specific Populations (8.4)*].

3 DOSAGE FORMS AND STRENGTHS

2 mg Injection: 2 mg/0.4 mL naloxone hydrochloride solution in a pre-filled auto-injector. Each EVZIO 2 mg delivers 2 mg naloxone hydrochloride injection (0.4 mL).

4 CONTRAINDICATIONS

EVZIO is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Recurrent Respiratory and Central Nervous System Depression

The duration of action of most opioids may exceed that of EVZIO resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms. Therefore, it is necessary to seek emergency medical assistance immediately after delivering the first dose of EVZIO. Keep the patient under continued surveillance, and administer additional doses of EVZIO as necessary [see *Dosage and Administration* (2.2)]. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

5.2 Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses of naloxone hydrochloride may be required to antagonize buprenorphine because the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor [see *Dosage and Administration* (2.3)]. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

5.3 Precipitation of Severe Opioid Withdrawal

The use of EVZIO in patients who are opioid dependent may precipitate an acute abstinence syndrome characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may include the following signs and symptoms: convulsions, excessive crying and hyperactive reflexes. Monitor patients for the development of the signs and symptoms of opioid withdrawal.

Abrupt postoperative reversal of opioid depression after using naloxone hydrochloride may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, after use of naloxone hydrochloride, monitor patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in an appropriate healthcare setting. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Precipitation of Severe Opioid Withdrawal [see *Warnings and Precautions* (5.3)]

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The following adverse reactions were observed in EVZIO clinical studies. In two pharmacokinetic studies with a total of 54 healthy adult subjects exposed to 0.4 mg EVZIO, 0.8 mg EVZIO (two 0.4 mg EVZIOs) or 2 mg EVZIO, adverse reactions occurring in more than one subject were dizziness and injection site erythema.

The following adverse reactions have been identified during post-approval use of naloxone hydrochloride in the post-operative setting. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: 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 [*see Warnings and Precautions (5.3)*].

Other events that have been reported in post-marketing use of EVZIO include agitation, disorientation, confusion, and anger.

Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated an acute withdrawal syndrome. Signs and symptoms have included: 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 [*see Warnings and Precautions (5.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on naloxone use in pregnant women are not sufficient to inform a drug-associated risk. However, there are risks to the fetus of the opioid-dependent mother with use of naloxone [*see Clinical Considerations*]. In animal reproduction studies, no embryotoxic or teratogenic effects were observed in mice and rats treated with naloxone hydrochloride during the period of organogenesis at doses equivalent to 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg [*see Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Naloxone hydrochloride crosses the placenta, and may precipitate withdrawal in the fetus as well as in the opioid-dependent mother [*see Warnings and Precautions (5.3)*]. The fetus should be evaluated for signs of distress after EVZIO is used. Careful monitoring is needed until the fetus and mother are stabilized.

Data

Animal Data

Naloxone hydrochloride was administered during organogenesis to mice and rats at doses 4-times and 8-times, respectively, the dose of 10 mg/day given to a 50 kg human (when based on body surface area or mg/m²). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.

8.2 Lactation

Risk Summary

There is no information regarding the presence of naloxone in human milk, or the effects of naloxone on the breastfed infant or on milk production. Studies in nursing mothers have shown that naloxone does not affect prolactin or oxytocin hormone levels. Naloxone is minimally orally bioavailable. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVZIO and any potential adverse effects on the breastfed infant from EVZIO or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of EVZIO (for intramuscular and subcutaneous use) have been established in pediatric patients of all ages for the emergency treatment of known or suspected opioid overdose. Use of naloxone hydrochloride in all pediatric patients is supported by adult bioequivalence studies coupled with evidence from the safe and effective use of another naloxone hydrochloride injectable product. No pediatric studies were conducted for EVZIO.

Absorption of naloxone hydrochloride following subcutaneous or intramuscular administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds appropriately to naloxone hydrochloride injection, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.

In opioid-dependent pediatric patients, (including neonates), administration of naloxone hydrochloride may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. Unlike acute opioid withdrawal in adults, acute opioid withdrawal in neonates manifesting as seizures may be life-threatening if not recognized and properly treated. Other signs and symptoms in neonates may include excessive crying and hyperactive reflexes. In these settings where it may be preferable to avoid the abrupt precipitation of acute opioid withdrawal symptoms, consider use of an alternative, naloxone hydrochloride product that can be dosed according to weight and titrated to effect. [*see Warnings and Precautions (5.3)*].

In pediatric patients under the age of one year, the caregiver should pinch the thigh muscle while administering EVZIO. Carefully observe the administration site for evidence of residual needle parts, signs of infection, or both. [*see Dosing Information (2.2)*].

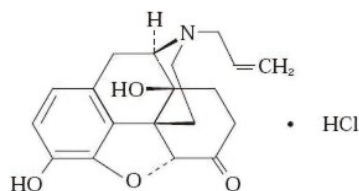
8.5 Geriatric Use

Geriatric patients have a greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Therefore, the systemic exposure of naloxone can be higher in these patients.

Clinical studies of naloxone hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11 DESCRIPTION

EVZIO (naloxone hydrochloride injection, USP) is a pre-filled, single-use auto-injector. EVZIO is not made with natural rubber latex. Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following structure:



$C_{19}H_{21}NO_4 \cdot HCl$

M.W. 363.84

Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Each 0.4 mL of EVZIO contains 2 mg naloxone hydrochloride, 3.34 mg of sodium chloride, hydrochloric acid to adjust pH, and water for injection. The pH range is 3.0 to 4.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naloxone hydrochloride is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites.

Naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation, and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

12.2 Pharmacodynamics

When naloxone hydrochloride is administered intravenously, the onset of action is generally apparent within two minutes. The time to onset of action is shorter for intravenous compared to subcutaneous or intramuscular routes of administration.

The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride.

12.3 Pharmacokinetics

In a pharmacokinetic study in 30 healthy subjects, a single 0.4 mg subcutaneous or intramuscular naloxone injection administered using EVZIO provides equivalent naloxone AUC and 15% greater naloxone C_{\max} in comparison to a single 0.4 mg subcutaneous or intramuscular naloxone injection administered using a standard syringe.

Following a single 0.4 mg EVZIO injection, the median T_{\max} of naloxone was reached at 0.25 hours (range 0.08 to 1.23 hours), with a mean C_{\max} value of 1.24 (51.4% CV) ng/mL. The mean plasma half-life of naloxone in healthy adults was 1.28 (38.0% CV) hours. In the same study, following administration of a single dose of 0.4 mg naloxone injection using a standard syringe, the median T_{\max} was 0.33 hours (range 0.08 to 2.03 hours) and the mean C_{\max} value was 1.07 (45.1% CV) ng/mL. The mean plasma half-life was 1.36 (23.5% CV) hours.

A second pharmacokinetic study in 24 healthy subjects using a crossover design, evaluated a single 0.4 mg EVZIO injection, a single 2 mg EVZIO injection, and two 0.4 mg EVZIO injections administered two minutes apart (0.8 mg naloxone hydrochloride total). The pharmacokinetic parameters obtained in this study are shown in Table 1 and the plasma concentration time profiles of naloxone are in Figure 1.

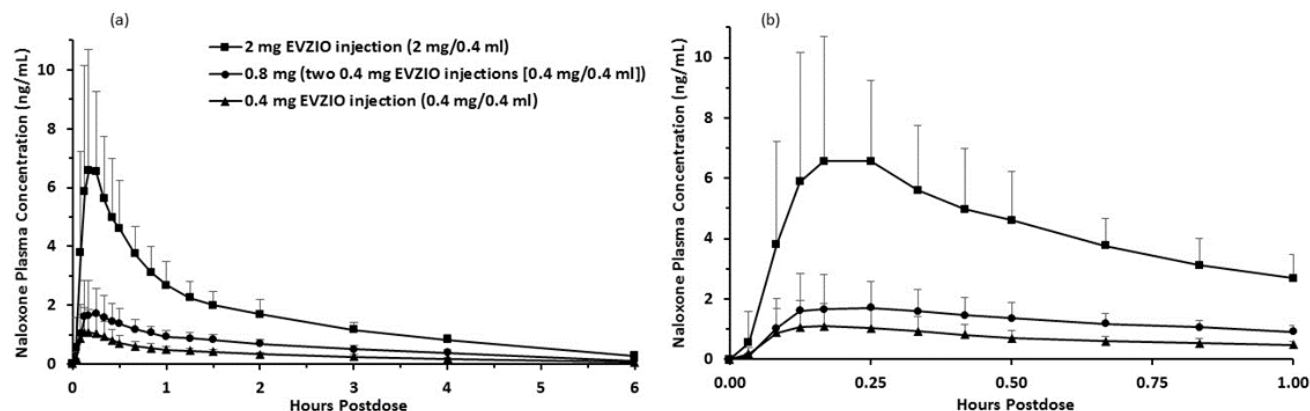
Table 1 Mean Pharmacokinetic Parameters (%CV) for Naloxone Following EVZIO (Naloxone HCl) Intramuscular/Subcutaneous Administration to Healthy Subjects

Parameter	0.4 mg EVZIO (N=24)	0.8 mg (two 0.4 mg EVZIO) (N=24)	2 mg EVZIO (N=24)
T_{\max} (h) [†]	0.25 (0.09, 0.84)	0.21 (0.09, 0.85)	0.25 (0.13, 0.67)
C_{\max} (ng/mL)	1.33 (62.9)	2.16 (47.4)	7.91 (45.8)
AUC _{0-t} (ng.h/mL)	1.82 (16.0)	3.50 (19.8)	9.66 (15.4)
AUC _{0-inf} (ng.h/mL)	2.00 (16.3) ^{††}	3.78 (19.1) ^{††}	10.33 (15.2)
$T_{1/2}$ (h)	1.58 (28.9) ^{††}	1.52 (23.7) ^{††}	1.53 (25.0)

[†] T_{\max} reported as median (minimum, maximum)

^{††} N=23 for AUC_{0-inf} and $T_{1/2}$

Figure 1 Mean \pm SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intramuscular/Subcutaneous Administration using EVZIO



Distribution

Following parenteral administration, naloxone is distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

Elimination

Following a single 0.4 mg EVZIO injection, the mean plasma half-life of naloxone in healthy adults was 1.58 (28.9% CV) hours and 1.53 (25% CV) hours following a single 2 mg EVZIO injection. In a neonatal study of naloxone injection, the mean (\pm SD) plasma half-life was observed to be 3.1 (\pm 0.5) hours.

Metabolism

Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucuronide as the major metabolite.

Excretion

After an oral or intravenous dose, about 25-40% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed.

Mutagenesis

Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.

Impairment of Fertility

Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m²), demonstrated no adverse effect of naloxone hydrochloride on fertility.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Carton containing two EVZIO (naloxone hydrochloride injection, USP) 2 mg auto-injectors and a single Trainer for EVZIO - NDC 60842-051-01

16.2 Storage and Handling

Store EVZIO in the outer case provided.

Store at controlled room temperature 15°C to 25°C (59°F to 77°F) excursions permitted between 4°C and 40°C (between 39°F and 104°F).

Before using, check to make sure the solution in the auto-injector is not discolored. Replace EVZIO if the solution is discolored or contains a precipitate.

17 PATIENT COUNSELING INFORMATION

Advise the patient and family members or caregivers to read the FDA-approved patient labeling (*Patient Information and Instructions for Use*).

Instruct patients and their family members or caregivers to:

- Become familiar with the following information contained in the carton as soon as they receive EVZIO:
 - EVZIO Instructions for Use
 - Trainer for EVZIO Instructions for Use
 - Trainer for EVZIO
- Become familiar with the device labeling color scheme of EVZIO and the Trainer for EVZIO
 - The 2 mg dosage form of EVZIO is blue and purple.
 - The Trainer for EVZIO is black and white.
- Practice using the Trainer before EVZIO is needed.
 - Each EVZIO can only be used one time; however, Trainer for EVZIO can be re-used for training purposes and its red safety guard can be removed and replaced.
 - Both EVZIO and Trainer for EVZIO incorporate the electronic voice instruction system.

- It is recommended that patients and caregivers become familiar with the Trainer for EVZIO provided and read the *Instructions for Use*; however, untrained caregivers or family members should still attempt to use EVZIO during a suspected opioid overdose while awaiting definitive emergency medical care.

Recognition of Opioid Overdose

Instruct the patients and their family members or caregivers how to recognize the signs and symptoms of an opioid overdose requiring the use of EVZIO such as the following:

- Extreme sleepiness - inability to awaken a patient verbally or upon a firm sternal rub.
- Breathing problems - this can range from slow or shallow breathing to no breathing in a patient who cannot be awakened.
- Other signs and symptoms that may accompany sleepiness and breathing problems include the following:
 - Extremely small pupils (the black circle in the center of the colored part of the eye) sometimes called “pinpoint pupils.”
 - Slow heartbeat and/or low blood pressure.

Risk of Recurrent Respiratory and Central Nervous System Depression

Instruct patients and their family members or caregivers that since the duration of action of most opioids may exceed that of EVZIO, they must seek immediate emergency medical assistance after the first dose of EVZIO and keep the patient under continued surveillance [*see Dosage and Administration (2.2), Warnings and Precautions (5.3)*].

Limited Efficacy for/with Partial Agonists or Mixed Agonist/Antagonists

Instruct patients and their family members or caregivers that the reversal of respiratory depression caused by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine, may be incomplete and may require higher doses of naloxone hydrochloride or repeated administration of EVZIO [*see Dosage and Administration (2.2), Warnings and Precautions (5.3)*].

Precipitation of Severe Opioid Withdrawal

Instruct patients and their family members or caregivers that the use of EVZIO in patients who are opioid dependent may precipitate an acute abstinence syndrome characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In neonates, opioid withdrawal may be life threatening if not recognized and properly treated, and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes [*see Warnings and Precautions (5.3, Adverse Reactions (6))*].

Administration Instructions

Instruct patients and their family members or caregivers about the following important information:

- Make sure EVZIO is present whenever persons may be intentionally or accidentally exposed to an opioid to treat serious opioid overdose (i.e., opioid emergencies).
- Administer EVZIO as quickly as possible if a patient is unresponsive and an opioid overdose is suspected, even when in doubt, because prolonged respiratory depression may result in damage to the central nervous system or death. **EVZIO is not a substitute for emergency medical care** [see *Dosage and Administration (2.1)*].
- EVZIO is user actuated and may be administered through clothing [e.g., pants, jeans, etc.] if necessary.
- Inject EVZIO while pressing into the anterolateral aspect of the thigh. In pediatric patients less than 1 year of age, pinch the thigh muscle while administering EVZIO.
- Upon actuation, EVZIO automatically inserts the needle intramuscularly or subcutaneously, delivers the naloxone, and retracts the needle fully into its housing. The needle is not visible before, during, or after injection.
- Each EVZIO can only be used one time.
- If the electronic voice instruction system on EVZIO does not work properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions on its label.
- The electronic voice instructions are independent of activating EVZIO and it is not necessary to wait for the voice instructions to be completed prior to moving to the next step in the injection process.
- Post-injection, the black base locks in place, a red indicator appears in the viewing window and electronic visual and audible instructions signal that EVZIO has delivered the intended dose of naloxone hydrochloride.
- EVZIO's red safety guard should not be replaced under any circumstances. However, the Trainer is designed for re-use and its red safety guard can be removed and replaced.
- Periodically visually inspect the naloxone solution through the viewing window. If the solution is discolored, cloudy, or contains solid particles, replace it with a new EVZIO.
- Replace EVZIO before its expiration date.

Manufactured for:

kaleo, Inc.

Richmond, VA 23219

*For California Only: This product uses batteries containing Perchlorate Material – special handling may apply. See www.dtsc.ca.gov/hazardouswaste/perchlorate

This product may be covered by one or more U.S. patents or pending patent applications. See www.kaleopharma.com/pat for details.

PATIENT INFORMATION
EVZIO® (EVV-zee-oh)
(naloxone hydrochloride injection)
Auto-Injector
for Intramuscular or Subcutaneous Use

You and your caregivers should read this Patient Information leaflet before an opioid emergency happens. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about EVZIO?

EVZIO is used to temporarily reverse the effects of opioid medicines. The medicine in EVZIO has no effect in people who are not taking opioid medicines. Always carry EVZIO with you in case of an opioid emergency.

- Use EVZIO right away if you or your caregiver think signs or symptoms of an opioid emergency are present, even if you are not sure, because an opioid emergency can cause severe injury or death. Signs and symptoms of an opioid emergency may include:
 - unusual sleepiness and you are not able to awaken the person with a loud voice or rubbing firmly on the middle of their chest (sternum)
 - breathing problems including slow or shallow breathing in someone difficult to awaken or they look like they are not breathing
 - the black circle in the center of the colored part of the eye (pupil) is very small, sometimes called “pinpoint pupils” in someone difficult to awaken
- Family members, caregivers, or other people who may have to use EVZIO in an opioid emergency should know where EVZIO is stored and how to give EVZIO before an opioid emergency happens.
- **Get emergency medical help right away after using the first dose of EVZIO.** Rescue breathing or CPR (cardiopulmonary resuscitation) may be given while waiting for emergency medical help.
- The signs and symptoms of an opioid emergency can return within several minutes after EVZIO is given. If this happens, give additional injections using a new EVZIO auto-injector every 2 to 3 minutes and continue to closely watch the person until emergency help is received.

What is EVZIO?

- EVZIO is a prescription medicine used in adults and children for the treatment of an opioid emergency such as an overdose or a possible opioid overdose with signs of breathing problems and severe sleepiness or not being able to respond.
- EVZIO is to be given right away and does not take the place of emergency medical care. Get emergency medical help right away after the first dose of EVZIO, even if the person wakes up.
- EVZIO is safe and effective in children for known or suspected opioid overdose.

Who should not use EVZIO?

Do not use EVZIO if you are allergic to naloxone hydrochloride or any of the ingredients in EVZIO. See the end of this leaflet for a complete list of ingredients in EVZIO.

What should I tell my healthcare provider before using EVZIO?

Before using EVZIO, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems
- are pregnant or plan to become pregnant. Use of EVZIO may cause withdrawal symptoms in your unborn baby. Your unborn baby should be examined by a healthcare provider right away after you use EVZIO.

Tell your healthcare provider about the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use EVZIO?

Read the “Instructions for Use” at the end of this Patient Information leaflet for detailed information about the right way to use EVZIO.

- You should use EVZIO exactly as prescribed by your healthcare provider.
- Each EVZIO auto-injector contains only 1 dose of medicine.
- EVZIO should be injected into the muscle or skin of the outer thigh. It can be injected through clothing if needed.
- Caregivers should pinch the thigh muscle while injecting EVZIO into a child under the age of one.
- A Trainer for EVZIO with a separate “Trainer Instructions for Use” leaflet is included with EVZIO. For additional training information and video instructions go to www.EVZIO.com or call 1-855-773-8946.
 - Practice with the Trainer for EVZIO before an opioid emergency happens to make sure you are able to safely use the real EVZIO in an emergency.
 - The Trainer for EVZIO does not contain a needle or medicine. It can be reused to practice your injection.
 - The red safety guard can be removed and replaced on the Trainer for EVZIO.

What are the possible side effects of EVZIO?

EVZIO may cause serious side effects, including:

- **Sudden opioid withdrawal symptoms.** In someone who has been using opioids regularly, opioid withdrawal symptoms can happen suddenly after receiving EVZIO and may include:
 - body aches
 - fever
 - sweating
 - runny nose
 - sneezing
 - goose bumps
 - yawning
 - weakness
 - shivering or trembling
 - nervousness
 - restlessness or irritability
 - diarrhea
 - nausea or vomiting
 - stomach cramping
 - increased blood pressure
 - increased heart rate

Common side effects of EVZIO include dizziness and injection site redness.

In infants under 4 weeks old who have been receiving opioids regularly, sudden opioid withdrawal may be life-threatening if not treated the right way. Signs and symptoms include: seizures, crying more than usual and increased reflexes.

These are not all of the possible side effects of EVZIO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EVZIO?

- Store EVZIO at room temperature between 59°F to 77°F (15°C to 25°C).
- Keep EVZIO in its outer case until ready to use.
- Occasionally check EVZIO through the viewing window of the auto-injector. The solution should be clear. If the EVZIO solution is discolored, cloudy, or contains solid particles, replace it with a new EVZIO.
- Your EVZIO has an expiration date. Replace it before the expiration date.

Keep EVZIO and all medicines out of the reach of children.

General information about the safe and effective use of EVZIO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EVZIO for a condition for which it was not prescribed. You can ask your pharmacist or healthcare provider for information about EVZIO that is written for health professionals.

What are the ingredients in EVZIO?

Active ingredient: naloxone hydrochloride

Inactive ingredients: sodium chloride, hydrochloric acid to adjust pH, and water

EVZIO is not made with natural rubber latex.

Manufactured for kaleo, Inc., Richmond, VA, 23219

For more information, go to www.EVZIO.com or call 1-855-773-8946

Instructions for Use
EVZIO® (EVV-zee-oh)
(naloxone hydrochloride injection)
Auto-Injector

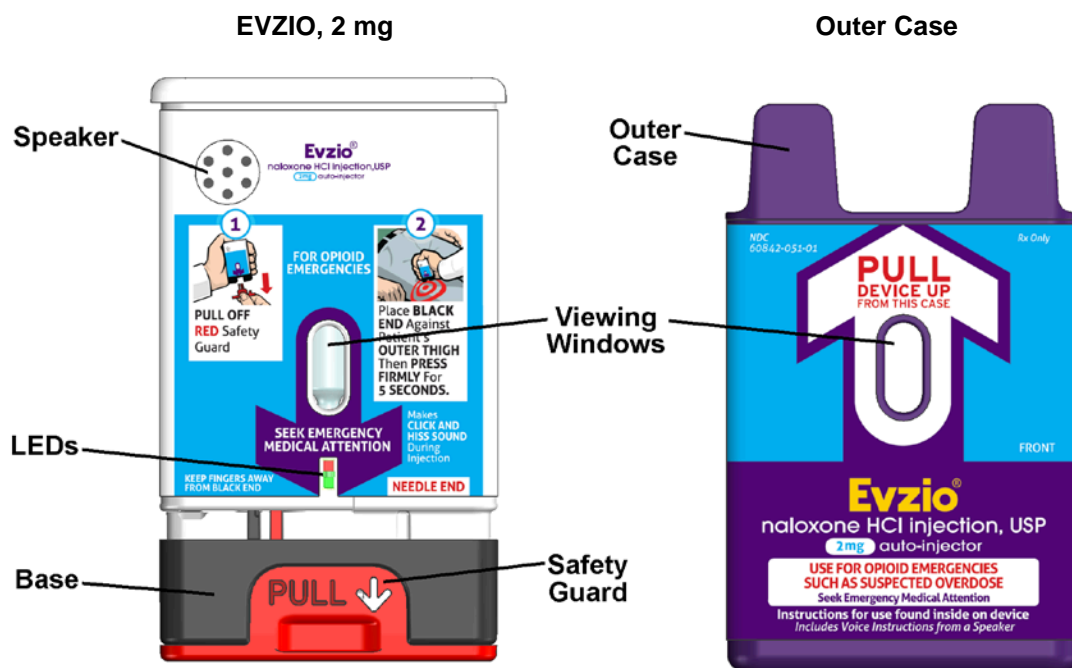
Read the Instructions for Use that comes with EVZIO before using it. Talk to your healthcare provider if you or your caregivers have any questions about the use of EVZIO.

Automated voice instructions

EVZIO has a speaker that provides voice instructions to help guide you through each step of the injection. See Figure A. If the voice instructions do not work for any reason, EVZIO will still work. If this happens, use EVZIO as instructed below and follow the written instructions on the EVZIO auto-injector label.

EVZIO Parts

Figure A

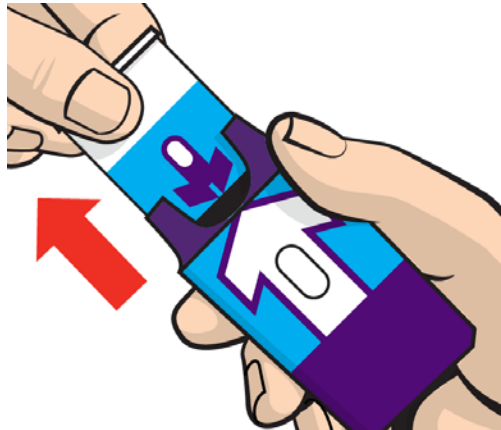


You do not need to assemble your EVZIO. EVZIO comes already assembled for use.

How to use EVZIO

Step 1. Pull EVZIO from the outer case. See Figure B.

Figure B

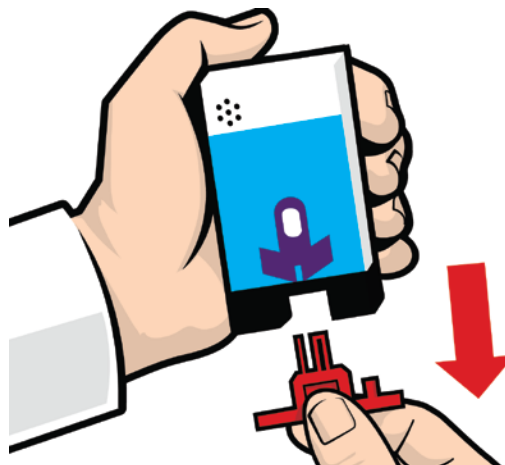


Do not go to Step 2 (Do not remove the **Red** safety guard) until you are ready to use EVZIO. **If you are not ready to use EVZIO, put it back in the outer case for later use.**

Step 2. Pull off the **Red** safety guard. See Figure C.

To reduce the chance of an accidental injection, do not touch the **Black** base of the auto-injector, which is where the needle comes out.

Figure C



If an accidental injection happens, get medical help right away.

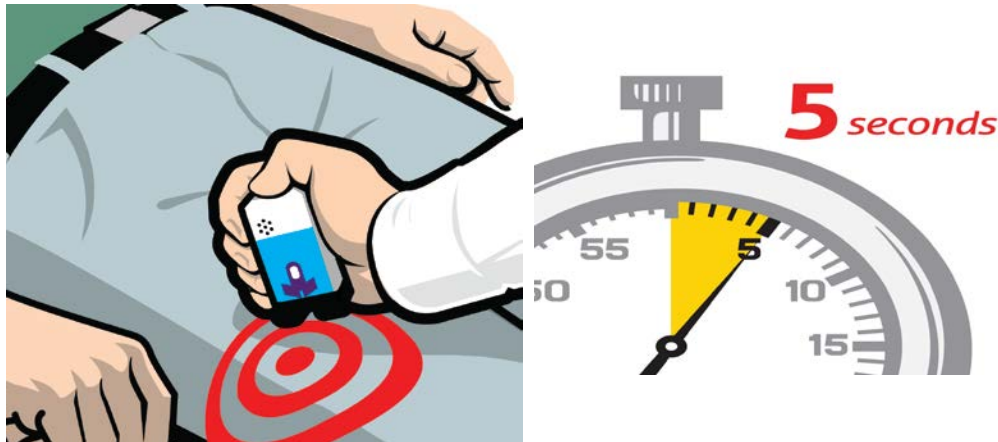
Note: The **Red** safety guard is made to fit tightly. **Pull firmly to remove.**

Do not replace the Red safety guard after it is removed.

Step 3. Place the **Black** end of EVZIO against the outer thigh, through clothing, if needed. **Press firmly** and hold in place for 5 seconds. See Figure D.

If you give EVZIO to an infant less than 1 year old, pinch the middle of the outer thigh before you give EVZIO and continue to pinch while you give EVZIO.

Figure D



Note: EVZIO makes a distinct sound (click and hiss) when it is pressed against the thigh. This is normal and means that EVZIO is working correctly. Keep EVZIO firmly pressed on the thigh for 5 seconds after you hear the click and hiss sound. The needle will inject and then retract back up into the EVZIO auto-injector and is not visible after use.

Step 4. After using EVZIO, get emergency medical help right away.

If symptoms return after an injection with EVZIO, an additional injection using another EVZIO may be needed. Give additional injections using a new EVZIO auto-injector every 2 to 3 minutes and continue to closely watch the person until emergency help is received. **EVZIO does not take the place of emergency medical care.**

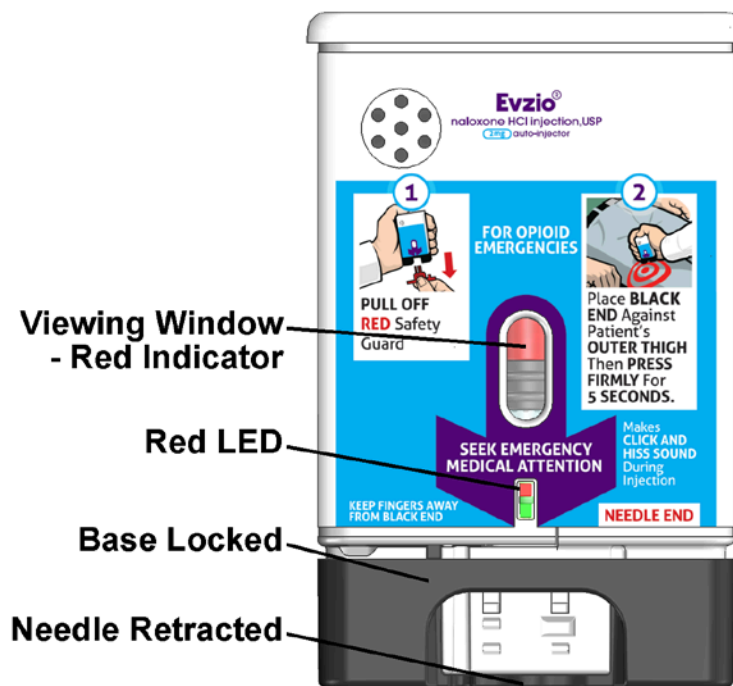
EVZIO cannot be reused. After use, place the auto-injector back into its outer case. Do not replace the **Red** safety guard.

How to know that EVZIO has been used. See Figure E.

- The **Black** base will lock into place.
- The voice instruction system will state that EVZIO has been used and the LED will blink red.
- The **Red** safety guard cannot be replaced.
- The viewing window will no longer be clear. You will see a red indicator.

Figure E

Used EVZIO



What to do after EVZIO has been used:

- Get emergency medical help right away.
- Put the used EVZIO back into its outer case.
- Do not throw away the EVZIO in household trash. Do not recycle EVZIO.
- Used EVZIO should be taken to a healthcare setting for proper disposal in a sharps container.

There may be local or state laws about how to throw away used auto-injectors.*

*For California Only: This product uses batteries containing Perchlorate Material – special handling may apply. See www.dtsc.ca.gov/hazardouswaste/perchlorate

How should I store EVZIO?

- Store EVZIO at room temperature between 59°F to 77°F (15°C to 25°C).
- Keep EVZIO in its outer case until ready to use.
- Occasionally check EVZIO through the viewing window of the auto-injector. The solution should be clear. If the EVZIO solution is discolored, cloudy, or contains solid particles, replace it with a new EVZIO.
- Your EVZIO has an expiration date. Replace it before the expiration date.

Keep EVZIO and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for: kaleo, Inc., Richmond, VA 23219

Revised: 10/2016

Trainer for EVZIO®
Trainer Instructions for Use

Important:

The Trainer for EVZIO Does Not contain a needle or medicine. Always carry your real EVZIO with you in case of an opioid emergency.

Tell your family, friends, co-workers or other individuals who may need to use EVZIO during an opioid emergency-where you keep your EVZIO.

Important Information about the Trainer for EVZIO:

Inside your Trainer for EVZIO are:

- batteries
- a speaker that will make a beeping sound and that produces electronic voice instructions
- red and green blinking lights

The Trainer for EVZIO batteries are made to last for over 1,000 demonstrations or practices.

If the electronic voice instructions do not work properly, the Trainer for EVZIO can still be used for demonstration or practice. If this happens, use the instructions below and follow the written instructions on the Trainer for EVZIO label.

What is the Trainer for EVZIO?

- The Trainer for EVZIO does not contain a needle or medicine and can be reused to practice your injection.
- Practice with the Trainer for EVZIO before an opioid emergency happens to make sure you are able to safely use the real EVZIO in an emergency.
- A Trainer for EVZIO comes with each EVZIO prescription so that you and your caregiver can practice and demonstrate how to use EVZIO.

Figure A

<p style="text-align: center;">Trainer for EVZIO</p> <div data-bbox="289 384 690 688"> </div> <p style="text-align: center;">Trainer Trainer Outer Case</p>	<p>Trainer for EVZIO:</p> <ul style="list-style-type: none"> • is inside a white and black outer case • does not contain a needle or medicine • can be reused (the Red safety guard can be placed back on the Black base after use)
<p style="text-align: center;">EVZIO 2 mg</p> <div data-bbox="297 825 690 1129"> </div> <p style="text-align: center;">EVZIO 2 mg EVZIO 2 mg Outer Case</p>	<p>EVZIO 2 mg:</p> <ul style="list-style-type: none"> • is inside a blue and purple outer case • contains a needle and medicine • cannot be reused (the Red safety guard cannot be placed back on the Black base after it is removed) • has an expiration date

In case of an opioid overdose or possible opioid overdose emergency, use the real EVZIO and not the Trainer for EVZIO.

Who should practice using the Trainer for EVZIO?

Anyone who may need to help you with EVZIO in case of an opioid overdose or possible overdose emergency should practice using the Trainer for EVZIO.

Have them practice using the Trainer for EVZIO and review the Patient Information leaflet included in the packaging with your prescription of EVZIO.

For more information and video instructions on the use of EVZIO, go to <http://www.EVZIO.com> or call 1-855-77-EVZIO.

Practicing with the Trainer for EVZIO

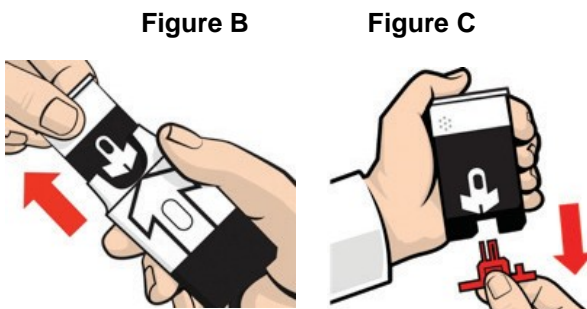
- Practice with the Trainer for EVZIO before an opioid emergency happens to make sure you are able to safely use the real EVZIO in the case of an opioid overdose or possible overdose emergency.
- You and your caregivers should practice every day for the first week after you receive your Trainer for EVZIO, and then at least 1 time each week, to help you feel familiar with using EVZIO quickly and safely during an opioid overdose or possible opioid overdose emergency. Even when you are familiar with using the Trainer for EVZIO, continue to practice using it often.

How to use the Trainer for EVZIO

- Even though the Trainer for EVZIO does not have a needle and contains no medicine, it works the same way as the real EVZIO.
- Just like the real EVZIO, the Trainer for EVZIO contains an electronic voice instruction system to help guide you through each step of the injection. If the voice instructions do not work for any reason, you can still use the Trainer for EVZIO to practice using the instructions below and following the written instructions on the Trainer for EVZIO.
- The Trainer for EVZIO has the same blinking red and green lights as the real EVZIO. These blinking lights help provide visual cues for each voice instruction and step.

Follow these steps to practice using the Trainer for EVZIO

1. **Pull the Trainer for EVZIO from the outer case.** See Figure B.
2. **Pull off Red safety guard.** See Figure C.



Note: The **Red** safety guard is made to fit tight similar to the safety guard on EVZIO. **Pull firmly to remove.**

3. Place **Black** end of the Trainer for EVZIO against the middle of the outer thigh (through clothing, if needed), then press firmly, and hold in place for 5 seconds. See Figure D.

Figure D



Only practice using the middle of the outer thigh. The outer thigh is where you would inject with the real EVZIO.

Note: The Trainer for EVZIO makes a distinct sound (click and hiss) when you press it against the outer thigh. This is the same sound that is made with the real EVZIO. This is normal and indicates EVZIO is working correctly. Do not pull the Trainer for EVZIO away from the leg when you hear the click and hiss sound.

4. After practicing, reset the Trainer for EVZIO:

- Replace the Red safety guard. See Figure E.
- Slide the Trainer for EVZIO all the way back into the white outer case to reset the electronic voice system. See Figure F.

Figure E



Figure F



Note: Do not hold the **Black** base when replacing the **Red** safety guard. If you do this, the **Black** base may not reset properly and may prevent you from inserting the **Red** safety guard into the **Black** base. If this happens, remove the **Red** safety guard and repeat Step 4 above.

Leave the Trainer for EVZIO in its outer case for at least 5 seconds between each time you practice to allow the electronic voice system to reset.

How should I dispose of the Trainer for EVZIO?

The Trainer for EVZIO contains electronics and lithium coin cell batteries, and should be disposed of in the correct manner. Follow your State and local environmental regulations for disposal.

For California Only: This product uses batteries containing Perchlorate Material- special handling may apply. See www.dtsc.ca.gov/hazardouswaste/perchlorate

For more information or questions about the Trainer for EVZIO, go to www.EVZIO.com or call 1-855-773-8946.

How should I store the Trainer for EVZIO?

- Store the Trainer for EVZIO at room temperature between 59°F to 77°F (15°C to 25°C).
- Store the Trainer for EVZIO in its outer case.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for kaleo, Inc. Richmond, VA 23219

Revised: **10/2016**

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

-----RECENT MAJOR CHANGES-----

Dosage and Administration, Dosing in Adults and Pediatric Patients (2.2) 01/2017

-----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)
- Administration of a single spray of NARCAN Nasal Spray 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: 2 mg and 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: 01/2017

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2.2 Dosing in Adults and Pediatric Patients

2.3 Dosing Modifications due to Partial Agonists or Mixed Agonist/Antagonists

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

5.1 Risk of Recurrent Respiratory and Central Nervous System Depression

5.2 Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

5.3 Precipitation of Severe Opioid Withdrawal

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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

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

Limitations of Use:

Restrict prescription of NARCAN Nasal Spray 2 mg to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

NARCAN Nasal Spray is for intranasal use only.

No additional device assembly is required.

Because treatment of suspected opioid overdose must be performed by someone other than the patient, instruct the prescription recipient to inform those around them about the presence of NARCAN Nasal Spray and the *Instructions for Use*.

Instruct the patient or caregiver to read the *Instructions for Use* at the time they receive a prescription for NARCAN Nasal Spray. Emphasize the following instructions to the patient or caregiver:

- Administer NARCAN Nasal Spray as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death. Since the duration of action of most opioids exceeds that of naloxone hydrochloride and the suspected opioid overdose may occur outside of supervised medical settings, seek immediate emergency medical assistance, keep the patient under continued surveillance until emergency personnel arrive, and administer repeated doses of NARCAN Nasal Spray, as necessary. Always seek emergency medical assistance in the event of a suspected, potentially life-threatening opioid emergency after administration of the first dose of NARCAN Nasal Spray.
- Additional doses of NARCAN Nasal Spray may be required until emergency medical assistance becomes available.
- Do not attempt to reuse NARCAN Nasal Spray. Each NARCAN Nasal Spray contains a single dose of naloxone and cannot be reused.
- Re-administer NARCAN Nasal Spray, using a new nasal spray, every 2 to 3 minutes if the patient does not respond or responds and then relapses into respiratory depression.

- Administer NARCAN Nasal Spray in alternate nostrils with each dose.
- Administer NARCAN Nasal Spray according to the printed instructions on the device label and the *Instructions for Use*.
- Place the patient in the supine position. Prior to administration, be sure the device nozzle is inserted in either nostril of the patient, and provide support to the back of the neck to allow the head to tilt back. **Do not prime or test the device prior to administration.**
- To administer the dose press firmly on the device plunger.
- Remove the device nozzle from the nostril after use.
- Turn patient on their side as shown in the *Instructions for Use* and call for emergency medical assistance immediately after administration of the first dose of NARCAN Nasal Spray.

2.2 Dosing in Adults and Pediatric Patients

Initial Dosing

The recommended initial dose of NARCAN Nasal Spray in adults and pediatric patients is one spray delivered by intranasal administration into one nostril.

Repeat Dosing

Seek emergency medical assistance as soon as possible after administering the first dose of NARCAN Nasal Spray.

The requirement for repeat doses of NARCAN Nasal Spray depends upon the amount, type, and route of administration of the opioid being antagonized.

Administer NARCAN Nasal Spray in alternate nostrils with each dose.

If the patient responds to NARCAN Nasal Spray and relapses back into respiratory depression before emergency assistance arrives, administer an additional dose of NARCAN Nasal Spray using a new NARCAN Nasal Spray and continue surveillance of the patient.

If the desired response is not obtained after 2 or 3 minutes, administer an additional dose of NARCAN Nasal Spray using a new NARCAN Nasal Spray. If there is still no response and additional doses are available, administer additional doses of NARCAN Nasal Spray every 2 to 3 minutes using a new NARCAN Nasal Spray with each dose until emergency medical assistance arrives.

Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

2.3 Dosing Modifications due to Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and require higher doses of naloxone

hydrochloride or repeated administration of NARCAN Nasal Spray using a new nasal spray [*see Warnings and Precautions (5.2)*].

3 DOSAGE FORMS AND STRENGTHS

NARCAN Nasal Spray is supplied as a single-dose intranasal spray containing 2 mg or 4 mg of naloxone hydrochloride in 0.1 mL.

4 CONTRAINDICATIONS

NARCAN Nasal Spray is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Recurrent Respiratory and Central Nervous System Depression

The duration of action of most opioids may exceed that of NARCAN Nasal Spray resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms. Therefore, it is necessary to seek emergency medical assistance immediately after administration of the first dose of NARCAN Nasal Spray and to keep the patient under continued surveillance. Administer additional doses of NARCAN Nasal Spray if the patient is not adequately responding or responds and then relapses back into respiratory depression, as necessary [*see Dosage and Administration (2.2)*]. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

5.2 Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses of naloxone hydrochloride may be required to antagonize buprenorphine because the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor [*see Dosage and Administration (2.3)*]. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

5.3 Precipitation of Severe Opioid Withdrawal

The use of NARCAN Nasal Spray in patients who are opioid-dependent may precipitate opioid withdrawal characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes. Monitor the patient for the development of the signs and symptoms of opioid withdrawal.

There are limited data to inform if the 2 mg dose of NARCAN Nasal Spray will avoid precipitation of severe opioid withdrawal in the setting of opioid dependence. However, the 2

mg dose may not provide an adequate and timely reversal in persons who may be exposed to an overdose of a potent or very high dose of opioids.

Abrupt postoperative reversal of opioid depression after using naloxone hydrochloride may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, after use of naloxone hydrochloride, monitor patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in an appropriate healthcare setting. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. In these settings, consider use of an alternative, naloxone-containing product that can be titrated to effect and, where applicable, dosed according to weight. [*see Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Precipitation of Severe Opioid Withdrawal [*see Warnings and Precautions (5.3)*]

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The following adverse reactions were observed in a NARCAN Nasal Spray clinical study.

In a pharmacokinetic study of 30 healthy adult volunteers exposed to one spray of NARCAN Nasal Spray in one nostril or two sprays of NARCAN Nasal Spray, one in each nostril, the most common adverse reactions were: increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, rhinalgia, and xeroderma.

The following adverse reactions have been identified primarily during post-approval use of naloxone hydrochloride in the post-operative setting. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: 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.

Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated an acute withdrawal syndrome. Signs and symptoms have included: 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 some patients, there may be aggressive behavior upon abrupt reversal of an opioid overdose. In the neonate, opioid withdrawal signs and symptoms also included convulsions, excessive crying, and hyperactive reflexes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on naloxone use in pregnant women are not sufficient to inform a drug-associated risk. However, there are clinical considerations [see *Clinical Considerations*]. In animal reproduction studies, no embryotoxic or teratogenic effects were observed in mice and rats treated with naloxone hydrochloride during the period of organogenesis at doses equivalent to 6-times and 12-times, respectively, a human dose of 8 mg/day (two NARCAN Nasal Sprays) based on body surface area comparison [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Naloxone hydrochloride crosses the placenta, and may precipitate withdrawal in the fetus, as well as in the opioid-dependent mother [see *Warnings and Precautions (5.3)*]. The fetus should be evaluated for signs of distress after NARCAN Nasal Spray is used. Careful monitoring is needed until the fetus and mother are stabilized.

Data

Animal Data

Naloxone hydrochloride was administered during organogenesis to mice and rats at subcutaneous doses up to 10 mg/kg/day (equivalent to 6-times and 12-times, respectively, a human dose of 8 mg (two NARCAN Nasal Sprays)) (based on body surface area comparison). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.

Pregnant female rats were administered 2 or 10 mg/kg naloxone subcutaneously from Gestation Day 15 to Postnatal day 21. There were no adverse effects on the offspring (up to 12-times a human dose of 8 mg/day (two NARCAN Nasal Sprays) based on body surface area comparison).

8.2 Lactation

Risk Summary

There is no information regarding the presence of naloxone in human milk, or the effects of naloxone on the breastfed infant or on milk production. Studies in nursing mothers have shown that naloxone does not affect prolactin or oxytocin hormone levels. Naloxone is minimally orally bioavailable.

8.4 Pediatric Use

The safety and effectiveness of NARCAN Nasal Spray have been established in pediatric patients of all ages for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression. Use of naloxone hydrochloride in all pediatric patients is supported by adult bioequivalence studies coupled with evidence from the safe and effective use of other naloxone hydrochloride drug products. No pediatric studies were conducted for NARCAN Nasal Spray.

Absorption of naloxone hydrochloride following intranasal administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds appropriately to naloxone hydrochloride, he/she must be carefully monitored for at least 24 hours, as a relapse may occur as naloxone hydrochloride is metabolized.

In opioid-dependent pediatric patients, (including neonates), administration of naloxone hydrochloride may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening, if not recognized, and should be treated according to protocols developed by neonatology experts [*see Warnings and Precautions (5.3)*].

In settings such as in neonates with known or suspected exposure to maternal opioid use, where it may be preferable to avoid the abrupt precipitation of opioid withdrawal symptoms, consider use of an alternate naloxone-containing product that can be dosed according to weight and titrated to effect.

Also, in situations where the primary concern is for infants at risk for opioid overdose, consider whether the availability of alternate naloxone-containing products may be better suited than NARCAN Nasal Spray.

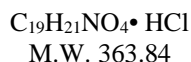
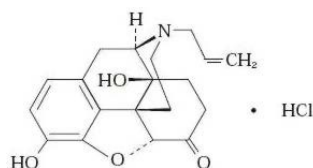
8.5 Geriatric Use

Geriatric patients have a greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Therefore, the systemic exposure of naloxone hydrochloride can be higher in these patients.

Clinical studies of naloxone hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11 DESCRIPTION

NARCAN (naloxone hydrochloride) Nasal Spray is a pre-filled, single dose intranasal spray. Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following structure:



Naloxone hydrochloride, an opioid antagonist, occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Each NARCAN Nasal Spray contains a 2 mg or 4 mg single dose of naloxone hydrochloride in a 0.1 mL (100 microliter) aqueous solution.

Inactive ingredients include benzalkonium chloride (preservative), disodium ethylenediaminetetraacetate (stabilizer), sodium chloride, hydrochloric acid to adjust pH, and purified water. The pH range is 3.5 to 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naloxone hydrochloride is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites.

Naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation, and hypotension. It can also reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

12.2 Pharmacodynamics

When naloxone hydrochloride is administered intravenously, the onset of action is generally apparent within two minutes. The time to onset of action is shorter for intravenous compared to subcutaneous or intramuscular routes of administration. The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride.

12.3 Pharmacokinetics

In a pharmacokinetic study in 30 healthy adult subjects, the relative bioavailability (BA) of one nasal spray in one nostril, consisting of a 2 mg total dose (0.1 mL of 20 mg/mL naloxone hydrochloride solution) and a 4 mg total dose (0.1 mL of 40 mg/mL naloxone hydrochloride solution), and two nasal sprays administered as one nasal spray in each nostril, consisting of a 4

mg total dose (0.1 mL of 20 mg/mL naloxone hydrochloride solution in each nostril) and an 8 mg total dose (0.1 mL of 40 mg/mL naloxone hydrochloride solution in each nostril), were compared to a single dose of 0.4 mg naloxone hydrochloride intramuscular injection. For intranasal administration, the subjects were instructed not to breathe through the nose during administration of the nasal spray, and remained fully supine for approximately one hour post-dose. For intramuscular administration, naloxone was administered as a single injection in the gluteus maximus muscle. The pharmacokinetic parameters obtained in the study are shown in Table 1.

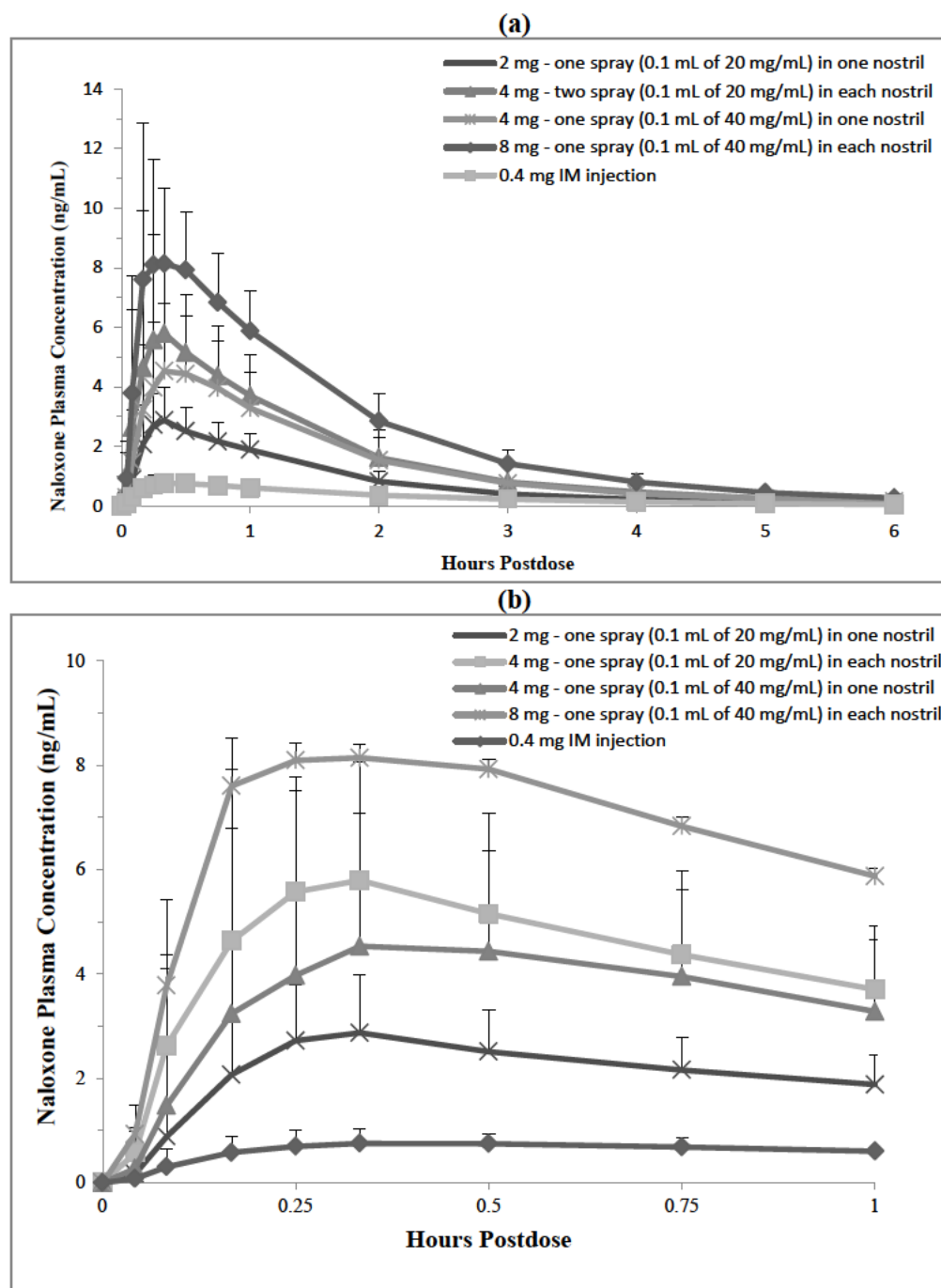
Table 1 Mean Pharmacokinetic Parameters (CV%) for Naloxone Following NARCAN (Naloxone HCl) Nasal Spray and Intramuscular Injection of Naloxone HCl to Healthy Subjects

Parameter	2 mg– One Nasal Spray in one nostril 20 mg/ml (N=29)	4 mg – Two Nasal Sprays, one in each nostril 20 mg/ml (N=29)	4 mg – One Nasal Spray in one nostril 40 mg/ml (N=29)	8 mg –Two Nasal Sprays, one in each nostril 40 mg/ml (N=29)	0.4 mg Intramuscular Injection (N=29)
t_{\max} (h) [†]	0.33 (0.25, 1.00)	0.33 (0.17, 0.57)	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
C_{\max} (ng/mL)	2.91 (35)	6.30 (34)	4.83 (43)	9.70 (36)	0.88 (31)
AUC _t (hr ng/mL)	4.60 (27)	9.64 (24)	7.87 (37)	15.3 (23)	1.75 (23)
AUC _{0-inf} (h*ng/mL)	4.66 (27)	9.74 (24)	7.95 (37)	15.5 (23)	1.79 (23)
$t_{1/2}$ (h)	1.85 (33)	2.19 (33)	2.08 (30)	2.10 (32)	1.24 (26)
Dose normalized Relative BA (%) vs. IM	51.7 (22)	54.0 (23)	44.2 (31) ^{††}	43.1 (24)	100

[†] t_{\max} reported as median (minimum, maximum)

^{††} N=28 for Relative BA.

Figure 1 Mean \pm SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intranasal Administration and Intramuscular Injection



The median naloxone t_{max} after intranasal administration of NARCAN Nasal Spray (one nasal spray in one nostril (2 mg or 4 mg) or two nasal sprays as one spray in each nostril (4 mg or 8 mg) was not significantly different compared to the 0.4 mg dose of naloxone hydrochloride intramuscular injection (Table 1).

The dose normalized relative bioavailability of one dose (2 mg or 4 mg) or two doses (4 mg or 8 mg) of NARCAN Nasal Spray as compared to the 0.4 mg dose of naloxone hydrochloride administered by intramuscular injection was 52%, 44%, 54%, and 43%, respectively.

Distribution

Following parenteral administration, naloxone is distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent, but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

Elimination

Following a single intranasal administration of NARCAN Nasal Spray (2 mg or 4 mg dose of naloxone hydrochloride), the mean plasma half-life of naloxone in healthy adults was approximately 1.85 (33% CV) hours and 2.08 (30% CV) hours; respectively, which was longer than that observed after administrations of a 0.4 mg naloxone hydrochloride intramuscular injection, where the half-life was 1.24 hours (26% CV). In a neonatal study of naloxone hydrochloride injection, the mean (\pm SD) plasma half-life was observed to be 3.1 (\pm 0.5) hours.

Metabolism

Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation, with naloxone-3-glucuronide as the major metabolite.

Excretion

After an oral or intravenous dose, about 25-40% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed.

Mutagenesis

Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.

Impairment of Fertility

Male rats were treated with 2 or 10 mg/kg naloxone for 60 days prior to mating. Female rats treated for 14-days prior to mating and throughout gestation with the same doses of naloxone (up to 12-times a human dose of 8 mg/day (two NARCAN Nasal Sprays) based on body surface area comparison). There was no adverse effect on fertility.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NARCAN Nasal Spray 2 mg is supplied as a carton containing four blister packages (NDC 69547-212-04) each with a single spray device and as a carton containing 24 blister packages (NDC 69547-212-24) each with a single spray device.

NARCAN Nasal Spray 4 mg is supplied as Carton containing two blister packages (NDC 69547-353-02) each with a single spray device.

NARCAN Nasal Spray is not made with natural rubber latex.

16.2 Storage and Handling

Store NARCAN Nasal Spray in the blister and cartons provided.

Store at controlled room temperature 59°F to 77°F (15°C to 25°C). Excursions permitted between 39°F to 104°F (4°C to 40°C). Do not freeze. Protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient and family members or caregivers to read the FDA-approved patient labeling (*Patient Information* and *Instructions for Use*).

Recognition of Opioid Overdose

Inform patients and their family members or caregivers about how to recognize the signs and symptoms of an opioid overdose such as the following:

- Extreme somnolence - inability to awaken a patient verbally or upon a firm sternal rub.
- Respiratory depression - this can range from slow or shallow respiration to no respiration in a patient who is unarousable.
- Other signs and symptoms that may accompany somnolence and respiratory depression include the following:
 - Miosis.
 - Bradycardia and/or hypotension.

Risk of Recurrent Respiratory and Central Nervous System Depression

Instruct patients and their family members or caregivers that, since the duration of action of most opioids may exceed that of NARCAN Nasal Spray, they must seek immediate emergency medical assistance after the first dose of NARCAN Nasal Spray and keep the patient under continued surveillance [*see Dosage and Administration (2.2), Warnings and Precautions (5.3)*].

Limited Efficacy for/with Partial Agonists or Mixed Agonist/Antagonists

Instruct patients and their family members or caregivers that the reversal of respiratory depression caused by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and may require higher doses of naloxone hydrochloride or repeated administration of NARCAN Nasal Spray, using a new nasal spray each time [see *Dosage and Administration (2.3), Warnings and Precautions (5.2)*].

Precipitation of Severe Opioid Withdrawal

Instruct patients and their family members or caregivers that the use of NARCAN Nasal Spray in patients who are opioid dependent may precipitate opioid withdrawal [see *Warnings and Precautions (5.3), Adverse Reactions (6)*].

Administration Instructions

Instruct patients and their family members or caregivers to:

- Ensure NARCAN Nasal Spray is present whenever persons may be intentionally or accidentally exposed to an opioid overdose (i.e., opioid emergencies).
- Administer NARCAN Nasal Spray as quickly as possible if a patient is unresponsive and an opioid overdose is suspected, even when in doubt, because prolonged respiratory depression may result in damage to the central nervous system or death. **NARCAN Nasal Spray is not a substitute for emergency medical care** [see *Dosage and Administration (2.1)*].
- Lay the patient on their back and administer NARCAN Nasal Spray into one nostril while providing support to the back of the neck to allow the head to tilt back [see *Dosage and Administration (2.1)*].
- Use each nasal spray only one time [see *Dosage and Administration (2.1)*].
- Turn patient on their side as shown in the *Instructions for Use* and call for emergency medical assistance immediately after administration of the first dose of NARCAN Nasal Spray. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance [see *Dosage and Administration (2.1)*].
- Monitor patients and re-administer NARCAN Nasal Spray using a new NARCAN Nasal Spray every 2 to 3 minutes, if the patient is not responding or responds and then relapses back into respiratory depression. Administer NARCAN Nasal Spray in alternate nostrils with each dose [see *Dosage and Administration (2.1)*].
- Replace NARCAN Nasal Spray before its expiration date.

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PATIENT INFORMATION
NARCAN (nar´ kan)
(naloxone hydrochloride)
Nasal Spray

You and your family members or caregivers should read this Patient Information leaflet before an opioid emergency happens. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about NARCAN Nasal Spray?

NARCAN Nasal Spray is used to temporarily reverse the effects of opioid medicines. The medicine in NARCAN Nasal Spray has no effect in people who are not taking opioid medicines. Always carry NARCAN Nasal Spray with you in case of an opioid emergency.

1. Use NARCAN Nasal Spray right away if you or your caregiver think signs or symptoms of an opioid emergency are present, even if you are not sure, because an opioid emergency can cause severe injury or death. Signs and symptoms of an opioid emergency may include:
 - unusual sleepiness and you are not able to awaken the person with a loud voice or by rubbing firmly on the middle of their chest (sternum)
 - breathing problems including slow or shallow breathing in someone difficult to awaken or who looks like they are not breathing
 - the black circle in the center of the colored part of the eye (pupil) is very small, sometimes called “pinpoint pupils,” in someone difficult to awaken
2. Family members, caregivers, or other people who may have to use NARCAN Nasal Spray in an opioid emergency should know where NARCAN Nasal Spray is stored and how to give NARCAN before an opioid emergency happens.
3. **Get emergency medical help right away after giving the first dose of NARCAN Nasal Spray.** Rescue breathing or CPR (cardiopulmonary resuscitation) may be given while waiting for emergency medical help.
4. The signs and symptoms of an opioid emergency can return after NARCAN Nasal Spray is given. If this happens, give another dose after 2 to 3 minutes using a new NARCAN Nasal Spray and watch the person closely until emergency help is received.

What is NARCAN Nasal Spray?

- NARCAN Nasal Spray is a prescription medicine used for the treatment of an opioid emergency such as an overdose or a possible opioid overdose with signs of breathing problems and severe sleepiness or not being able to respond.
- NARCAN Nasal Spray is to be given right away and does not take the place of emergency medical care. Get emergency medical help right away after giving the first dose of NARCAN Nasal Spray, even if the person wakes up.
- NARCAN Nasal Spray is safe and effective in children for known or suspected opioid overdose.

Who should not use NARCAN Nasal Spray?

Do not use NARCAN Nasal Spray if you are allergic to naloxone hydrochloride or any of the ingredients in NARCAN Nasal Spray. See the end of this leaflet for a complete list of ingredients in NARCAN Nasal Spray.

What should I tell my healthcare provider before using NARCAN Nasal Spray?

Before using NARCAN Nasal Spray, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems
- are pregnant or plan to become pregnant. Use of NARCAN Nasal Spray may cause withdrawal symptoms in your unborn baby. Your unborn baby should be examined by a healthcare provider right away after you use NARCAN Nasal Spray.
- are breastfeeding or plan to breastfeed. It is not known if NARCAN Nasal Spray passes into your breast milk.

Tell your healthcare provider about the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use NARCAN Nasal Spray?

Read the “Instructions for Use” at the end of this Patient Information leaflet for detailed information about the right way to use NARCAN Nasal Spray.

- Use NARCAN Nasal Spray exactly as prescribed by your healthcare provider.
- Each NARCAN Nasal Spray contains only 1 dose of medicine and cannot be reused.
- NARCAN Nasal Spray comes in a 2 mg and 4 mg strength. Your healthcare provider will prescribe the one that is right for you.
- Lay the person on their back. Support their neck with your hand and allow the head to tilt back before giving NARCAN Nasal Spray.
- NARCAN Nasal Spray should be given into one nostril.
- If additional doses are needed, give NARCAN Nasal Spray in the other nostril.

What are the possible side effects of NARCAN Nasal Spray?**NARCAN Nasal Spray may cause serious side effects, including:**

- **Sudden opioid withdrawal symptoms.** In someone who has been using opioids regularly, opioid withdrawal symptoms can happen suddenly after receiving NARCAN Nasal Spray and may include:
 - body aches
 - diarrhea
 - increased heart rate
 - fever
 - runny nose
 - sneezing
 - goose bumps
 - sweating
 - yawning
 - nausea or vomiting
 - nervousness
 - restlessness or irritability
 - shivering or trembling
 - stomach cramping
 - weakness
 - increased blood pressure

In infants under 4 weeks old who have been receiving opioids regularly, sudden opioid withdrawal may be life-threatening if not treated the right way. Signs and symptoms include: seizures, crying more than usual, and increased reflexes.

These are not all of the possible side effects of NARCAN Nasal Spray. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NARCAN Nasal Spray?

- Store NARCAN Nasal Spray at room temperature between 59°F to 77°F (15°C to 25°C). NARCAN Nasal Spray may be stored for short periods between 39°F to 104°F (4°C to 40°C).
- Do not freeze NARCAN Nasal Spray.
- Keep NARCAN Nasal Spray in its box until ready to use. Protect from light.
- Replace NARCAN Nasal Spray before the expiration date on the box.

Keep NARCAN Nasal Spray and all medicines out of the reach of children.**General information about the safe and effective use of NARCAN Nasal Spray.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NARCAN Nasal Spray for a condition for which it was not prescribed. You can ask your pharmacist or healthcare provider for information about NARCAN Nasal Spray that is written for health professionals.

What are the ingredients in NARCAN Nasal Spray?

Active ingredient: naloxone hydrochloride

Inactive ingredients: benzalkonium chloride (preservative), disodium ethylenediaminetetraacetate (stabilizer), sodium chloride, hydrochloric acid to adjust pH and sterile water

NARCAN Nasal Spray is not made with natural rubber latex.

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For more information, go to www.narcannasalspray.com or call 1-844-4NARCAN (1-844-462-7226).

This Patient Information has been approved by the U.S. Food and Drug Administration.

Issued: 01/2017

Instructions for Use NARCAN (nar' kan) (naloxone hydrochloride) Nasal Spray

You and your family members or caregivers should read the Instructions for Use that comes with NARCAN Nasal Spray before using it. Talk to your healthcare provider if you and your family members or caregivers have any questions about the use of NARCAN Nasal Spray.

Use NARCAN Nasal Spray for known or suspected opioid overdose in adults and children.

Important: For use in the nose only.

- **Do not remove or test the NARCAN Nasal Spray until ready to use.**
- **Each NARCAN Nasal Spray has 1 dose and cannot be reused.**
- **You do not need to prime NARCAN Nasal Spray.**

How to use NARCAN Nasal Spray:

Step 1. Lay the person on their back to receive a dose of NARCAN Nasal Spray.

Step 2. Remove NARCAN Nasal Spray from the box. Peel back the tab with the circle to open the NARCAN Nasal Spray.



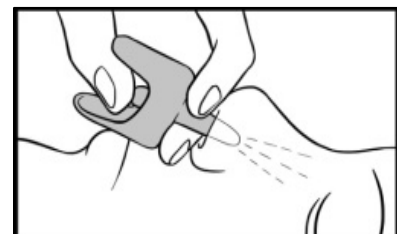
Step 3. Hold the NARCAN Nasal Spray with your thumb on the bottom of the plunger and your first and middle fingers on either side of the nozzle.



Step 4. Tilt the person's head back and provide support under the neck with your hand. Gently insert the tip of the nozzle into **one nostril** until your fingers on either side of the nozzle are against the bottom of the person's nose.



Step 5. Press the plunger firmly to give the dose of NARCAN Nasal Spray.



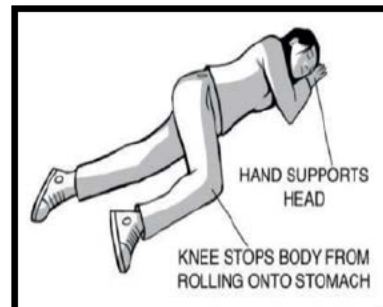
Step 6. Remove the NARCAN Nasal Spray from the

nostril after giving the dose.

What to do after NARCAN Nasal Spray has been used:

Step 7. Get emergency medical help right away.

- Move the person on their side (recovery position) after giving NARCAN Nasal Spray.
- Watch the person closely.
- If the person does not respond by waking up, to voice or touch, or breathing normally another dose may be given. NARCAN Nasal Spray may be dosed every 2 to 3 minutes, if available.
- Repeat **Steps 2 through 6** using a new NARCAN Nasal Spray to give another dose in the other nostril. If additional NARCAN Nasal Sprays are available, Steps 2 through 6 may be repeated every 2 to 3 minutes until the person responds or emergency medical help is received.



Step 8. Put the used NARCAN Nasal Spray back into its box.

Step 9. Throw away (dispose of) the used NARCAN Nasal Spray in a place that is away from children.

How should I store NARCAN Nasal Spray?

- Store NARCAN Nasal Spray at room temperature between 59°F to 77°F (15°C to 25°C). NARCAN Nasal Spray may be stored for short periods between 39°F to 104°F (4°C to 40°C).
- Do not freeze NARCAN Nasal Spray.
- Keep NARCAN Nasal Spray in the box until ready to use. Protect from light.
- Replace NARCAN Nasal Spray before the expiration date on the box.

Keep NARCAN Nasal Spray and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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For more information, go to www.narcannasalspray.com or call 1-844-4NARCAN (1-844-462-7226).

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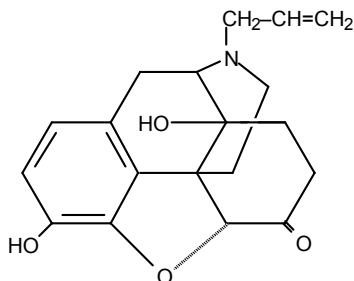
NARCAN[®]
(Naloxone Hydrochloride Injection, USP)

Opioid Antagonist


R_x only

DESCRIPTION

NARCAN (naloxone hydrochloride injection, USP), an opioid antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



•HCl

NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5 α -epoxy-3, 14 - dihydroxy 
morphinan-6-one hydrochloride

Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

NARCAN injection is available as a sterile solution for intravenous, intramuscular and subcutaneous administration in three concentrations: 0.02 mg, 0.4 mg and 1 mg of naloxone hydrochloride per mL.

pH is adjusted to 3.5 ± 0.5 with hydrochloric acid.

The 0.02 mg/mL strength is an unpreserved, paraben-free formulation containing 9 mg/mL sodium chloride.

The 0.4 mg/mL vial contains 8.6 mg/mL of sodium chloride and 2 mg/mL of methylparaben and propylparaben as preservatives in a ratio of 9:1. The 0.4 mg/mL ampul is also available in an unpreserved, paraben-free formulation containing 9 mg/mL of sodium chloride.

The 1 mg/mL vial contains 8.35 mg/mL of sodium chloride and 2 mg/mL of methylparaben and propylparaben as preservatives in a ratio of 9:1. The 1 mg/mL ampul is also available in an unpreserved, paraben-free formulation containing 9 mg/mL of sodium chloride.

CLINICAL PHARMACOLOGY

Complete or Partial Reversal of Opioid Depression

NARCAN prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension. Also, NARCAN can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

NARCAN is an essentially pure opioid antagonist, i.e., it does not possess the “agonistic” or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.

NARCAN has not been shown to produce tolerance or cause physical or psychological dependence. In the presence of physical dependence on opioids, NARCAN will produce withdrawal symptoms. However, in the presence of opioid dependence, opiate withdrawal symptoms may appear within minutes of NARCAN administration and subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of NARCAN and to the degree and type of opioid dependence. While the mechanism of action of NARCAN is not fully understood, *in vitro* evidence suggests that NARCAN antagonizes opioid effects by competing for the μ , κ and σ opiate receptor sites in the CNS, with the greatest affinity for the μ receptor.

When NARCAN is administered intravenously (I.V.), the onset of action is generally apparent within two minutes. The onset of action is slightly less rapid when it is administered subcutaneously (S.C.) or intramuscularly (I.M.). The duration of action is dependent upon the dose and route of administration of NARCAN. Intramuscular administration produces a more prolonged effect than intravenous administration. Since the duration of action of NARCAN may be shorter than that of some opiates, the effects of the opiate may return as the effects of NARCAN dissipates. The requirement for repeat doses of NARCAN will also be dependent upon the amount, type and route of administration of the opioid being antagonized.

Adjunctive Use in Septic Shock

NARCAN has been shown in some cases of septic shock to produce a rise in blood pressure that may last up to several hours; however, this pressor response has not been demonstrated to improve patient survival. In some studies, treatment with NARCAN in the setting of septic shock has been associated with adverse effects, including agitation, nausea and vomiting, pulmonary edema, hypotension, cardiac arrhythmias, and seizures. The decision to use NARCAN in septic shock should be exercised with caution, particularly in patients who may have underlying pain or have previously received opioid therapy and may have developed opioid tolerance.

Because of the limited number of patients who have been treated, optimal dosage and treatment regimens have not been established.

PHARMACOKINETICS

Distribution

Following parenteral administration, NARCAN is rapidly distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

Metabolism and Elimination

NARCAN is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucuronide as the major metabolite. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours. After an oral or intravenous dose, about 25-40% of the drug is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

INDICATIONS AND USAGE

NARCAN is indicated 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, butorphanol, and cyclazocine. NARCAN is also indicated for diagnosis of suspected or known acute opioid overdose.

NARCAN may be useful as an adjunctive agent to increase blood pressure in the management of septic shock (see **CLINICAL PHARMACOLOGY; Adjunctive Use in Septic Shock**).

CONTRAINDICATIONS

NARCAN is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients in NARCAN.

WARNINGS

Drug Dependence

NARCAN should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include, but are not limited to, the following: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In the neonate, opioid withdrawal may also include: convulsions, excessive crying, and hyperactive reflexes.

Repeat Administration

The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some opioids may exceed that of NARCAN.

Respiratory Depression due to Other Drugs

NARCAN is not effective against respiratory depression due to non-opioid drugs and in the management of acute toxicity caused by levopropoxyphene. Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete or require higher doses of naloxone. If an incomplete response occurs, respirations should be mechanically assisted as clinically indicated.

PRECAUTIONS

General

In addition to NARCAN, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute opioid poisoning.

Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death. Excessive doses of NARCAN in postoperative patients may result in significant reversal of analgesia and may cause agitation (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION; Usage in Adults-Postoperative Opioid Depression**). Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation, and pulmonary edema. It has been suggested that the pathogenesis of pulmonary edema associated with the use of NARCAN is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

Drug Interactions

Large doses of naloxone are required to antagonize buprenorphine since the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression. The barbiturate methohexital appears to block the acute onset of withdrawal symptoms induced by naloxone in opiate addicts.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals to assess the carcinogenic potential of NARCAN have not been conducted. NARCAN was weakly positive in the Ames mutagenicity and in the *in vitro* human lymphocyte chromosome aberration test but was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in the *in vivo* rat bone marrow chromosome aberration study. Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to NARCAN.

Use in Pregnancy

Teratogenic Effects: Pregnancy Category C:

Teratology studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to NARCAN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NARCAN should be used during pregnancy only if clearly needed.

Non-teratogenic Effects:

Risk-benefit must be considered before NARCAN is administered to a pregnant woman who is known or suspected to be opioid-dependent since maternal dependence may often be accompanied by fetal dependence. Naloxone crosses the placenta, and may precipitate withdrawal in the fetus as well as in the mother. Patients with mild to moderate hypertension who receive naloxone during labor should be carefully monitored as severe hypertension may occur.

Use in Labor and Delivery

It is not known if NARCAN (naloxone hydrochloride injection, USP) affects the duration of labor and/or delivery. However, published reports indicated that administration of naloxone during labor did not adversely affect maternal or neonatal status.

Nursing Mothers

It is not known whether NARCAN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NARCAN is administered to a nursing woman.

Pediatric Use

NARCAN (naloxone hydrochloride injection, USP) may be administered intravenously, intramuscularly or subcutaneously in children and neonates to reverse the effects of opiates. The American Academy of Pediatrics, however, does not endorse subcutaneous or intramuscular administration in opiate intoxication since absorption may be erratic or delayed. Although the opiate-intoxicated child responds dramatically to NARCAN, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.

When NARCAN is given to the mother shortly before delivery, the duration of its effect lasts only for the first two hours of neonatal life. It is preferable to administer NARCAN

directly to the neonate if needed after delivery. NARCAN has no apparent benefit as an additional method of resuscitation in the newly born infant with intrauterine asphyxia which is not related to opioid use.

Usage in Pediatric Patients and Neonates for Septic Shock:

The safety and effectiveness of NARCAN in the treatment of hypotension in pediatric patients and neonates with septic shock have not been established. One study of two neonates in septic shock reported a positive pressor response; however, one patient subsequently died after intractable seizures.

Geriatric Use

Clinical studies of NARCAN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Insufficiency/Failure

The safety and effectiveness of NARCAN in patients with renal insufficiency/failure have not been established in well-controlled clinical trials. Caution should be exercised when NARCAN is administered to this patient population.

Liver Disease

The safety and effectiveness of NARCAN in patients with liver disease have not been established in well-controlled clinical trials. Caution should be exercised when NARCAN is administered to patients with liver disease.

ADVERSE REACTIONS

Postoperative

The following adverse events have been associated with the use of NARCAN in postoperative patients: 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 NARCAN in postoperative patients may result in significant reversal of analgesia and may cause agitation (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION; Usage in Adults-Postoperative Opioid Depression**).

Opioid Depression

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death (see **PRECAUTIONS**).

Opioid Dependence

Abrupt reversal of opioid effects in persons who are physically dependent on opioids may precipitate an acute withdrawal syndrome which may include, but is not limited to, the

following signs and symptoms: 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 may also include: convulsions; excessive crying; hyperactive reflexes (see **WARNINGS**).

Adverse events associated with the postoperative use of NARCAN are listed by organ system and in decreasing order of frequency as follows:

Cardiac Disorders: pulmonary edema, cardiac arrest or failure, tachycardia, ventricular fibrillation, and ventricular tachycardia. Death, coma, and encephalopathy have been reported as sequelae of these events.

Gastrointestinal Disorders: vomiting, nausea

Nervous System Disorders: convulsions, paraesthesia, grand mal convulsion

Psychiatric Disorders: agitation, hallucination, tremulousness

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, respiratory depression, hypoxia

Skin and Subcutaneous Tissue Disorders: nonspecific injection site reactions, sweating

Vascular Disorders: hypertension, hypotension, hot flushes or flushing.

See also **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**; **Usage in Adults**; **Postoperative Opioid Depression**.

DRUG ABUSE AND DEPENDENCE

NARCAN is an opioid antagonist. Physical dependence associated with the use of NARCAN has not been reported. Tolerance to the opioid antagonist effect of NARCAN is not known to occur.

OVERDOSAGE

There is limited clinical experience with NARCAN overdose in humans.

Adult Patients

In one small study, volunteers who received 24 mg/70 kg did not demonstrate toxicity. In another study, 36 patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m²/min) of NARCAN followed immediately by 2 mg/kg/hr for 24 hours. Twenty-three patients experienced adverse events associated with naloxone use, and naloxone was discontinued in seven patients because of adverse effects. The most serious adverse events were: seizures (2 patients), severe hypertension (1), and hypotension and/or bradycardia (3).

At doses of 2 mg/kg in normal subjects, cognitive impairment and behavioral symptoms, including irritability, anxiety, tension, suspiciousness, sadness, difficulty concentrating, and lack of appetite have been reported. In addition, somatic symptoms, including dizziness, heaviness, sweating, nausea, and stomachaches were also reported. Although complete information is not available, behavioral symptoms were reported to often persist for 2-3 days.

Pediatric Patients

Up to 11 doses of 0.2 mg of naloxone (2.2 mg) have been administered to children following overdose of diphenoxylate hydrochloride with atropine sulfate. Pediatric reports include a 2-1/2 year-old child who inadvertently received a dose of 20 mg of naloxone for treatment of respiratory depression following overdose with diphenoxylate hydrochloride with atropine sulfate. The child responded well and recovered without adverse sequelae. There is also a report of a 4-1/2 year-old child who received 11 doses during a 12-hour period, with no adverse sequelae.

Patient Management

Patients who experience a NARCAN overdose should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control center for the most up-to-date patient management information.

DOSAGE AND ADMINISTRATION

NARCAN may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration, which is recommended in emergency situations.

Since the duration of action of some opioids may exceed that of NARCAN, the patient should be kept under continued surveillance. Repeated doses of NARCAN should be administered, as necessary.

Intravenous Infusion

NARCAN may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2 mg of NARCAN in 500 mL of either solution provides a concentration of 0.004 mg/mL. Mixtures should be used within 24 hours. After 24 hours, the remaining unused mixture must be discarded. The rate of administration should be titrated in accordance with the patient's response.

NARCAN should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to NARCAN unless its effect on the chemical and physical stability of the solution has first been established.

General

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Usage in Adults

Opioid Overdose—Known or Suspected:

An initial dose of 0.4 mg to 2 mg of NARCAN may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions are not obtained, it may be repeated at two- to three-minute intervals. If no response is observed after 10 mg of NARCAN have been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Opioid Depression:

For the partial reversal of opioid depression following the use of opioids during surgery, smaller doses of NARCAN are usually sufficient. The dose of NARCAN should be titrated according to the patient's response. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.1 to 0.2 mg intravenously at two- to three-minute intervals to the desired degree of reversal, i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of NARCAN may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of NARCAN may be required within one- to two-hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of an opioid. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

Septic Shock:

The optimal dosage of NARCAN or duration of therapy for the treatment of hypotension in septic shock patients has not been established (see **CLINICAL PHARMACOLOGY**).

Usage in Children

Opioid Overdose—Known or Suspected:

The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, NARCAN may be administered I.M. or S.C. in divided doses. If necessary, NARCAN can be diluted with sterile water for injection.

Postoperative Opioid Depression:

Follow the recommendations and cautions under **Adult Postoperative Depression**. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.005 mg to 0.01 mg intravenously at two- to three-minute intervals to the desired degree of reversal.

Usage in Neonates

Opioid-induced Depression:

The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines for postoperative opioid depression.

HOW SUPPLIED

NARCAN (naloxone hydrochloride injection, USP) for intravenous, intramuscular, and subcutaneous administration is available as:

Multiple Dose Vials

0.4 mg/mL	10 mL multiple dose vial-box of 1, NDC 63481-365-05
1 mg/mL	10 mL multiple dose vial-box of 1, NDC 63481-368-05

Preservative-Free Ampules

0.02 mg/mL	2 mL unit dose ampule-box of 10, NDC 63481-359-10
0.4 mg/mL	1 mL unit dose ampule-box of 10, NDC 63481-358-10
1 mg/mL	2 mL unit dose ampule-box of 10, NDC 63481-377-10

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]. Protect from light.

Store in carton until contents have been used.

Manufactured for:

Endo Pharmaceuticals Inc.

Chadds Ford, Pennsylvania 19317



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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

OXYCONTIN® (oxycodone hydrochloride) extended-release tablets, for oral use, CII

Initial U.S. Approval: 1950

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- OXYCONTIN exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)
- To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.3)
- Accidental ingestion of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone. (5.3)
- Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone. (5.5, 7, 12.3)
- 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. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.6, 7)

-----RECENT MAJOR CHANGES-----

Boxed Warning 09/2018
Warnings and Precautions (5.2) 09/2018

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

OXYCONTIN is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use

- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- OXYCONTIN is not indicated as an as-needed (prn) analgesic. (1)

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

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)

- OXYCONTIN 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Instruct patients to swallow tablets intact and not to cut, break, chew, crush, or dissolve tablets (risk of potentially fatal dose). (2.1, 5.1)
- Instruct patients to take tablets one at a time, with enough water to ensure complete swallowing immediately after placing in mouth. (2.1, 5.10)
- Do not abruptly discontinue OXYCONTIN in a physically dependent patient. (2.9)

Adults: For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg tablets orally every 12 hours. See full prescribing information for instructions on conversion from opioids to OXYCONTIN, titration and maintenance of therapy. (2.2, 2.3, 2.5)

Pediatric Patients 11 Years of Age and Older

- For use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days immediately preceding dosing with OXYCONTIN. (2.4)
 - See full prescribing information for instructions on conversion from opioids to OXYCONTIN, titration and maintenance of therapy. (2.4, 2.5)
- Geriatric Patients: In debilitated, opioid non-tolerant geriatric patients, initiate dosing at one third to one half the recommended starting dosage and titrate carefully. (2.7, 8.5)
- Patients with Hepatic Impairment: Initiate dosing at one third to one half the recommended starting dosage and titrate carefully. (2.8, 8.6)

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

Extended-release tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg. (3)

-----CONTRAINDICATIONS-----

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to oxycodone (4)

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

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of OXYCONTIN in patients with circulatory shock. (5.9)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of OXYCONTIN in patients with impaired consciousness or coma. (5.10)
- Risk of Obstruction in Patients who have Difficulty Swallowing or have Underlying GI Disorders that may Predispose them to Obstruction: Consider use of an alternative analgesic. (5.11)

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

Most common adverse reactions (incidence >5%) were constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- CNS Depressants: Concomitant use may cause hypotension, profound sedation, respiratory depression, coma, and death. If co-administration is

required and the decision to begin OXYCONTIN is made, start with 1/3 to 1/2 the recommended starting dosage, consider using a lower dosage of the concomitant CNS depressant, and monitor closely. (2.6, 5.6, 7)

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue OXYCONTIN if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with OXYCONTIN because they may reduce analgesic effect of OXYCONTIN or precipitate withdrawal symptoms. (5.14, 7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of morphine. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)

-----USE IN SPECIFIC POPULATIONS-----

Pregnancy: May cause fetal harm. (8.1)

Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

OXYCONTIN[®] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OXYCONTIN and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions* (5.1)].

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [see *Warnings and Precautions* (5.2)]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of OXYCONTIN. Monitor for respiratory depression, especially during initiation of OXYCONTIN or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole; crushing, chewing, or dissolving OXYCONTIN tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone [see *Warnings and Precautions* (5.3)].

Accidental Ingestion

Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone [see *Warnings and Precautions* (5.3)].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of

neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions* (5.4)].

Cytochrome P450 3A4 Interaction

The concomitant use of OXYCONTIN with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OXYCONTIN and any CYP3A4 inhibitor or inducer [see *Warnings and Precautions* (5.5), *Drug Interactions* (7), *Clinical Pharmacology* (12.3)].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

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 [see *Warnings and Precautions* (5.6), *Drug Interactions* (7)].

- Reserve concomitant prescribing of OXYCONTIN and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

1 INDICATIONS AND USAGE

OXYCONTIN is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations [see *Warnings and Precautions* (5.1)], reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- OXYCONTIN is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

OXYCONTIN should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

OXYCONTIN 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. Adult patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].
- Initiate the dosing regimen for each patient individually; taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [*see Warnings and Precautions (5.1)*].
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with OXYCONTIN and adjust the dosage accordingly [*see Warnings and Precautions (5.3)*].

Instruct patients to swallow OXYCONTIN tablets whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth [*see Patient Counseling Information (17)*]. Instruct patients not to pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth [*see Warnings and Precautions (5.11)*]. Cutting, breaking, crushing, chewing, or dissolving OXYCONTIN tablets will result in uncontrolled delivery of oxycodone and can lead to overdose or death [*see Warnings and Precautions (5.1)*].

OXYCONTIN is administered orally every 12 hours.

2.2 Initial Dosage in Adults who are not Opioid-Tolerant

The starting dosage for patients who are not opioid tolerant is OXYCONTIN 10 mg orally every 12 hours.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression [*see Warnings and Precautions (5.3)*].

2.3 Conversion from Opioids to OXYCONTIN in Adults

Conversion from Other Oral Oxycodone Formulations to OXYCONTIN

If switching from other oral oxycodone formulations to OXYCONTIN, administer one half of the patient's total daily oral oxycodone dose as OXYCONTIN every 12 hours.

Conversion from Other Opioids to OXYCONTIN

Discontinue all other around-the-clock opioid drugs when OXYCONTIN therapy is initiated.

There are no established conversion ratios for conversion from other opioids to OXYCONTIN defined by clinical trials. Initiate dosing using OXYCONTIN 10 mg orally every 12 hours.

It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxycodone dosage and manage an adverse reaction due to an overdose. While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioids.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to OXYCONTIN.

Conversion from Methadone to OXYCONTIN

Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Transdermal Fentanyl to OXYCONTIN

Treatment with OXYCONTIN can be initiated after the transdermal fentanyl patch has been removed for at least 18 hours. Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OXYCONTIN every 12 hours for each 25 mcg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCONTIN, as there is limited documented experience with this conversion.

2.4 Initial Dosage in Pediatric Patients 11 Years and Older

The following dosing information is for use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least five consecutive days. For the two days immediately preceding dosing with OXYCONTIN, patients must be taking a minimum of 20 mg per day of oxycodone or its equivalent. OXYCONTIN is not appropriate for use in pediatric patients requiring less than a 20 mg total daily dose. Table 1, based on clinical trial experience, displays the conversion factor when switching pediatric patients 11 years and older (under the conditions described above) from opioids to OXYCONTIN.

Discontinue all other around-the-clock opioid drugs when OXYCONTIN therapy is initiated.

There is substantial inter-patient variability in the relative potency of different opioid drugs and formulations. Therefore, a conservative approach is advised when determining the total daily dosage of OXYCONTIN. It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to

overestimate the 24-hour oral oxycodone requirements and manage an adverse reaction due to an overdose.

Consider the following when using the information in Table 1.

- This is not a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion from one of the listed oral opioid analgesics to OXYCONTIN.
- The table cannot be used to convert from OXYCONTIN to another opioid. Doing so will result in an over-estimation of the dose of the new opioid and may result in fatal overdose.
- The formula for conversion from prior opioids, including oral oxycodone, to the daily dose of OXYCONTIN is mg per day of prior opioid x factor = mg per day of OXYCONTIN. Divide the calculated total daily dose by 2 to get the every-12-hour OXYCONTIN dose. If rounding is necessary, always round the dose down to the nearest OXYCONTIN tablet strength available.

Table 1: Conversion Factors When Switching Pediatric Patients 11 Years and Older to OXYCONTIN

Prior Opioid	Conversion Factor	
	Oral	Parenteral*
Oxycodone	1	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Morphine	0.5	3
Tramadol	0.17	0.2

*For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

Step #1: To calculate the estimated total OXYCONTIN daily dosage using Table 1:

- For pediatric patients taking a single opioid, sum the current total daily dosage of the opioid and then multiply the total daily dosage by the approximate conversion factor to calculate the approximate OXYCONTIN daily dosage.
- For pediatric patients on a regimen of more than one opioid, calculate the approximate oxycodone dose for each opioid and sum the totals to obtain the approximate OXYCONTIN daily dosage.

- For pediatric patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Step #2: If rounding is necessary, always round the dosage down to the nearest OXYCONTIN tablet strength available and initiate OXYCONTIN therapy with that dose. If the calculated OXYCONTIN total daily dosage is less than 20 mg, there is no safe strength for conversion and do not initiate OXYCONTIN.

Example conversion from a single opioid (e.g., hydrocodone) to OXYCONTIN: Using the conversion factor of 0.9 for oral hydrocodone in Table 1, a total daily hydrocodone dosage of 50 mg is converted to 45 mg of oxycodone per day or 22.5 mg of OXYCONTIN every 12 hours. After rounding down to the nearest strength available, the recommended OXYCONTIN starting dosage is 20 mg every 12 hours.

Step #3: Close observation and titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to OXYCONTIN. [see *Dosage and Administration (2.5)*] for important instructions on titration and maintenance of therapy.

There is limited experience with conversion from transdermal fentanyl to OXYCONTIN in pediatric patients 11 years and older. If switching from transdermal fentanyl patch to OXYCONTIN, ensure that the patch has been removed for at least 18 hours prior to starting OXYCONTIN. Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OXYCONTIN every 12 hours for each 25 mcg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCONTIN.

If using asymmetric dosing, instruct patients to take the higher dose in the morning and the lower dose in the evening.

2.5 Titration and Maintenance of Therapy in Adults and Pediatric Patients 11 Years and Older

Individually titrate OXYCONTIN to a dosage that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OXYCONTIN to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and adverse reactions, as well as monitoring for the development of addiction, abuse and misuse [see *Warnings and Precautions (5.1)*]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dosage adjustment of OXYCONTIN or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain

before increasing the OXYCONTIN dosage. Because steady-state plasma concentrations are approximated in 1 day, OXYCONTIN dosage may be adjusted every 1 to 2 days.

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline for pediatric patients 11 years and older, the total daily oxycodone dosage usually can be increased by 25% of the current total daily dosage. As a guideline for adults, the total daily oxycodone dosage usually can be increased by 25% to 50% of the current total daily dosage, each time an increase is clinically indicated.

2.6 Dosage Modifications with Concomitant Use of Central Nervous System Depressants

If the patient is currently taking a central nervous system (CNS) depressant and the decision is made to begin OXYCONTIN, start with one-third to one-half the recommended starting dosage of OXYCONTIN, consider using a lower dosage of the concomitant CNS depressant, and monitor patients for signs of respiratory depression, sedation, and hypotension [*see Warnings and Precautions (5.6), Drug Interactions (7)*].

2.7 Dosage Modifications in Geriatric Patients who are Debilitated and not Opioid-Tolerant

For geriatric patients who are debilitated and not opioid tolerant, start dosing patients at one-third to one-half the recommended starting dosage and titrate the dosage cautiously [*see Use in Specific Populations (8.5)*].

2.8 Dosage Modifications in Patients with Hepatic Impairment

For patients with hepatic impairment, start dosing patients at one-third to one-half the recommended starting dosage and titrate the dosage carefully. Monitor for signs of respiratory depression, sedation, and hypotension [*see Use in Specific Populations, (8.6), Clinical Pharmacology (12.3)*].

2.9 Discontinuation of OXYCONTIN

When the patient no longer requires therapy with OXYCONTIN, taper the dosage gradually, by 25% to 50% every 2 to 4 days, while monitoring for signs and symptoms of withdrawal. If a patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OXYCONTIN [*see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)*].

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg.

- 10 mg film-coated extended-release tablets (round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other)
- 15 mg film-coated extended-release tablets (round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other)
- 20 mg film-coated extended-release tablets (round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other)
- 30 mg film-coated extended-release tablets (round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other)
- 40 mg film-coated extended-release tablets (round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other)
- 60 mg film-coated extended-release tablets (round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other)
- 80 mg film-coated extended-release tablets (round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other)

4 CONTRAINDICATIONS

OXYCONTIN is contraindicated in patients with:

- Significant respiratory depression [*see Warnings and Precautions (5.3)*]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [*see Warnings and Precautions (5.7)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [*see Warnings and Precautions (5.12)*]
- Hypersensitivity (e.g., anaphylaxis) to oxycodone [*see Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

OXYCONTIN contains oxycodone, a Schedule II controlled substance. As an opioid, OXYCONTIN exposes users to the risks of addiction, abuse, and misuse. Because extended-release products such as OXYCONTIN deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present [*see Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OXYCONTIN. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing OXYCONTIN, and monitor all patients receiving OXYCONTIN for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as OXYCONTIN, but use in such patients necessitates intensive counseling about the risks and proper use of OXYCONTIN along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of OXYCONTIN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and death [*see Overdosage (10)*].

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OXYCONTIN. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling* authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG .
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint .

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see *Overdosage (10)*]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OXYCONTIN, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of OXYCONTIN.

To reduce the risk of respiratory depression, proper dosing and titration of OXYCONTIN are essential [see *Dosage and Administration (2)*]. Overestimating the OXYCONTIN dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCONTIN during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Use in Specific Populations (8.1)*, *Patient Counseling Information (17)*].

5.5 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of OXYCONTIN with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [see *Warnings and Precautions (5.3)*], particularly when an inhibitor is added after a stable dose of OXYCONTIN is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in OXYCONTIN-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using OXYCONTIN with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in OXYCONTIN-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of OXYCONTIN until stable drug effects are achieved [see *Drug Interactions (7)*].

Concomitant use of OXYCONTIN with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using OXYCONTIN with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [*see Drug Interactions (7)*].

5.6 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result if OXYCONTIN is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., non-benzodiazepines sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [*see Drug Interactions (7)*].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when OXYCONTIN is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [*see Drug Interactions (7), Patient Counseling Information (17)*].

5.7 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of OXYCONTIN in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: OXYCONTIN-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of OXYCONTIN [see *Warnings and Precautions* (5.3)].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see *Warnings and Precautions* (5.3)].

Monitor such patients closely, particularly when initiating and titrating OXYCONTIN and when OXYCONTIN is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions* (5.3, 5.6)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.9 Severe Hypotension

OXYCONTIN may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [see *Drug Interactions* (7)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of OXYCONTIN. In patients with circulatory shock, OXYCONTIN may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OXYCONTIN in patients with circulatory shock.

5.10 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), OXYCONTIN may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure.

Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with OXYCONTIN.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of OXYCONTIN in patients with impaired consciousness or coma.

5.11 Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen

There have been post-marketing reports of difficulty in swallowing OXYCONTIN tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick, or otherwise wet OXYCONTIN tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.

There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

5.12 Risks of Use in Patients with Gastrointestinal Conditions

OXYCONTIN is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The oxycodone in OXYCONTIN may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.13 Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in OXYCONTIN may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during OXYCONTIN therapy.

5.14 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including OXYCONTIN. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing OXYCONTIN, gradually taper the dosage [see *Dosage and Administration* (2.9)]. Do not abruptly discontinue OXYCONTIN [see *Drug Abuse and Dependence* (9.3)].

5.15 Risks of Driving and Operating Machinery

OXYCONTIN may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of OXYCONTIN and know how they will react to the medication [see *Patient Counseling Information* (17)].

5.16 Laboratory Monitoring

Not every urine drug test for “opioids” or “opiates” detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified “cut-off” value as “negative”. Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse [see *Warnings and Precautions* (5.1)]
- Life-Threatening Respiratory Depression [see *Warnings and Precautions* (5.3)]
- Neonatal Opioid Withdrawal Syndrome [see *Warnings and Precautions* (5.4)]
- Interactions With Benzodiazepines and Other CNS Depressants [see *Warnings and Precautions* (5.6)]
- Adrenal Insufficiency [see *Warnings and Precautions* (5.8)]
- Severe Hypotension [see *Warnings and Precautions* (5.9)]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions* (5.11, 5.12)]
- Seizures [see *Warnings and Precautions* (5.13)]
- Withdrawal [see *Warnings and Precautions* (5.14)]

6.1 Clinical Trial Experience

Adult Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OXYCONTIN was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OXYCONTIN in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

OXYCONTIN may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock [see *Overdosage (10)*].

The most common adverse reactions (>5%) reported by patients in clinical trials comparing OXYCONTIN with placebo are shown in Table 2 below:

TABLE 2: Common Adverse Reactions (>5%)

Adverse Reaction	OXYCONTIN (n=227) (%)	Placebo (n=45) (%)
Constipation	(23)	(7)
Nausea	(23)	(11)
Somnolence	(23)	(4)
Dizziness	(13)	(9)
Pruritus	(13)	(2)
Vomiting	(12)	(7)
Headache	(7)	(7)
Dry Mouth	(6)	(2)
Asthenia	(6)	-
Sweating	(5)	(2)

In clinical trials, the following adverse reactions were reported in patients treated with OXYCONTIN with an incidence between 1% and 5%:

Gastrointestinal disorders: abdominal pain, diarrhea, dyspepsia, gastritis

General disorders and administration site conditions: chills, fever

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: twitching

Psychiatric disorders: abnormal dreams, anxiety, confusion, dysphoria, euphoria, insomnia, nervousness, thought abnormalities

Respiratory, thoracic and mediastinal disorders: dyspnea, hiccups

Skin and subcutaneous tissue disorders: rash

Vascular disorders: postural hypotension

The following adverse reactions occurred in less than 1% of patients involved in clinical trials:

Blood and lymphatic system disorders: lymphadenopathy

Ear and labyrinth disorders: tinnitus

Eye disorders: abnormal vision

Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, stomatitis

General disorders and administration site conditions: withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema

Injury, poisoning and procedural complications: accidental injury

Investigations: ST depression

Metabolism and nutrition disorders: dehydration

Nervous system disorders: syncope, migraine, abnormal gait, amnesia, hyperkinesia, hypoesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perversion

Psychiatric disorders: depression, agitation, depersonalization, emotional lability, hallucination

Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention

Reproductive system and breast disorders: impotence

Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration

Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis

Clinical Trial Experience in Pediatric Patients 11 Years and Older

The safety of OXYCONTIN has been evaluated in one clinical trial with 140 patients 11 to 16 years of age. The median duration of treatment was approximately three weeks. The most frequently reported adverse events were vomiting, nausea, headache, pyrexia, and constipation.

Table 3 includes a summary of the incidence of treatment emergent adverse events reported in $\geq 5\%$ of patients.

Table 3: Incidence of Adverse Reactions Reported in $\geq 5.0\%$ Patients 11 to 16 Years

System Organ Class Preferred Term	11 to 16 Years (N=140) n (%)
Any Adverse Event $\geq 5\%$	71 (51)

GASTROINTESTINAL DISORDERS	56 (40)
Vomiting	30 (21)
Nausea	21 (15)
Constipation	13 (9)
Diarrhea	8 (6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	32 (23)
Pyrexia	15 (11)
METABOLISM AND NUTRITION DISORDERS	9 (6)
Decreased appetite	7 (5)
NERVOUS SYSTEM DISORDERS	37 (26)
Headache	20 (14)
Dizziness	12 (9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	23 (16)
Pruritus	8 (6)

The following adverse reactions occurred in a clinical trial of OXYCONTIN in patients 11 to 16 years of age with an incidence between $\geq 1.0\%$ and $< 5.0\%$. Events are listed within each System/Organ Class.

Blood and lymphatic system disorders: febrile neutropenia, neutropenia

Cardiac disorders: tachycardia

Gastrointestinal disorders: abdominal pain, gastroesophageal reflux disease

General disorders and administration site conditions: fatigue, pain, chills, asthenia

Injury, poisoning, and procedural complications: procedural pain, seroma

Investigations: oxygen saturation decreased, alanine aminotransferase increased, hemoglobin decreased, platelet count decreased, neutrophil count decreased, red blood cell count decreased, weight decreased

Metabolic and nutrition disorders: hypochloremia, hyponatremia

Musculoskeletal and connective tissue disorders: pain in extremity, musculoskeletal pain

Nervous system disorders: somnolence, hypoesthesia, lethargy, paresthesia

Psychiatric disorders: insomnia, anxiety, depression, agitation

Renal and urinary disorders: dysuria, urinary retention

Respiratory, thoracic, and mediastinal disorders: oropharyngeal pain

Skin and subcutaneous tissue disorders: hyperhidrosis, rash

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of extended-release oxycodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Abuse, addiction, aggression, amenorrhea, cholestasis, completed suicide, death, dental caries, increased hepatic enzymes, hyperalgesia, hypogonadism, hyponatremia, ileus, intentional overdose, mood altered, muscular hypertonia, overdose, palpitations (in the context of withdrawal), seizures, suicidal attempt, suicidal ideation, syndrome of inappropriate antidiuretic hormone secretion, and urticaria.

In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in OXYCONTIN.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see *Clinical Pharmacology* (12.2)].

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with OXYCONTIN.

Table 4: Clinically Significant Drug Interactions with OXYCONTIN

Inhibitors of CYP3A4 and CYP2D6	
<i>Clinical Impact:</i>	The concomitant use of OXYCONTIN and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of OXYCONTIN and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of OXYCONTIN is achieved [see <i>Warnings</i>

	<p>and Precautions (5.5)].</p> <p>After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease [see <i>Clinical Pharmacology</i> (12.3)], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.</p>
<i>Intervention:</i>	<p>If concomitant use is necessary, consider dosage reduction of OXYCONTIN until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.</p> <p>If a CYP3A4 inhibitor is discontinued, consider increasing the OXYCONTIN dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.</p>
<i>Examples</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
<i>Clinical Impact:</i>	<p>The concomitant use of OXYCONTIN and CYP3A4 inducers can decrease the plasma concentration of oxycodone [see <i>Clinical Pharmacology</i> (12.3)], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone [see <i>Warnings and Precautions</i> (5.5)].</p> <p>After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase [see <i>Clinical Pharmacology</i> (12.3)], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.</p>
<i>Intervention:</i>	If concomitant use is necessary, consider increasing the OXYCONTIN dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider OXYCONTIN dosage reduction and monitor for signs of respiratory depression.
<i>Examples:</i>	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see <i>Dosage and Administration</i> (2.6), <i>Warnings and Precautions</i> (5.6)].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue OXYCONTIN if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine

	reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions</i> (5.3)].
<i>Intervention:</i>	The use of OXYCONTIN is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
<i>Examples:</i>	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
<i>Clinical Impact:</i>	May reduce the analgesic effect of OXYCONTIN and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
<i>Clinical Impact:</i>	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of OXYCONTIN and/or the muscle relaxant as necessary.
Diuretics	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when OXYCONTIN is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see *Warnings and Precautions* (5.4)]. There are no available data with OXYCONTIN in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there was no embryo-fetal toxicity when

oxycodone hydrochloride was orally administered to rats and rabbits, during the period of organogenesis, at doses 1.3 to 40 times the adult human dose of 60 mg/day, respectively. In a pre- and postnatal toxicity study, when oxycodone was orally administered to rats, there was transiently decreased pup body weight during lactation and the early post-weaning period at the dose equivalent to an adult dose of 60 mg/day. In several published studies, treatment of pregnant rats with oxycodone hydrochloride at clinically relevant doses and below resulted in neurobehavioral effects in offspring [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.4)].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. OXYCONTIN is not recommended for use in women immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including OXYCONTIN, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Pregnant rats were treated with 0.5, 2, 4, and 8 mg/kg oxycodone hydrochloride (0.08, 0.3, 0.7, and 1.3 times the human daily dose of 60 mg/day, respectively based on a mg/m² basis) during the period of organogenesis. Oxycodone did not cause adverse effects to the fetus at exposures up to 1.3 times the human dose of 60 mg/day. The high dose produced maternal toxicity characterized by excessive gnawing on forelimbs and decreased body weight gain.

Pregnant rabbits were treated with 1, 5, 25, and 125 mg/kg oxycodone hydrochloride (0.3, 2, 8, and 40 times the human daily dose of 60 mg/day, respectively, based on a mg/m² basis) during the period of organogenesis. Oxycodone did not cause adverse effects to the fetus at exposures up to 40 times the human dose of 60 mg/day. The 25 mg/kg and 125 mg/kg doses high doses produced maternal toxicity characterized by decreased food consumption and body weight gain.

Pregnant rats were treated with 0.5, 2, and 6 mg/kg oxycodone hydrochloride (0.08, 0.32, and 1 times the human daily dose of 60 mg/kg, respective, based on a mg/m² basis, during the period of organogenesis through lactation. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to an adult human dose of 60 mg/day, on a mg/m² basis). However, body weight of these pups recovered.

In published studies, offspring of pregnant rats administered oxycodone hydrochloride during gestation have been reported to exhibit neurobehavioral effects including altered stress responses and increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3 times an adult human oral dose of 60 mg/day on a mg/m² basis), and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human oral dose of 60 mg/day on a mg/m² basis).

8.2 Lactation

Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfed infants for potential adverse reactions. Lactation studies have not been conducted with extended-release oxycodone, including OXYCONTIN, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with OXYCONTIN.

Clinical Considerations

Infants exposed to OXYCONTIN through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [*see Adverse Reactions (6.2), Clinical Pharmacology (12.2)*].

8.4 Pediatric Use

The safety and efficacy of OXYCONTIN have been established in pediatric patients ages 11 to 16 years. Use of OXYCONTIN is supported by evidence from adequate and well-controlled trials with OXYCONTIN in adults as well as an open-label study in pediatric patients ages 6 to 16 years. However, there were insufficient numbers of patients less than 11 years of age enrolled in this study to establish the safety of the product in this age group.

The safety of OXYCONTIN in pediatric patients was evaluated in 155 patients previously receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent on the two days immediately preceding dosing with OXYCONTIN. Patients were started on a total daily dose ranging between 20 mg and 100 mg depending on prior opioid dose.

The most frequent adverse events observed in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation [*see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Trials (14)*].

8.5 Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% [*see Clinical Pharmacology (12.3)*]. Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride controlled-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received oxycodone hydrochloride controlled-release tablets. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. However, a dosage reduction in debilitated, non-opioid-tolerant patients is recommended [*see Dosage and Administration (2.7)*].

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who are not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of OXYCONTIN slowly in these patients and monitor closely for signs of central nervous system and respiratory depression. [see *Warnings and Precautions* (5.7)].

Oxycodone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

A study of OXYCONTIN in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function [see *Clinical Pharmacology* (12.3)]. Therefore, a dosage reduction is recommended for these patients [see *Dosage and Administration* (2.8)]. Monitor closely for signs of respiratory depression, sedation, and hypotension.

8.7 Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function [see *Clinical Pharmacology* (12.3)]. Follow a conservative approach to dose initiation and adjust according to the clinical situation.

8.8 Sex Differences

In pharmacokinetic studies with OXYCONTIN, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OXYCONTIN contains oxycodone, a Schedule II controlled substance.

9.2 Abuse

OXYCONTIN contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol. OXYCONTIN can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions* (5.1)].

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

OXYCONTIN, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of OXYCONTIN

OXYCONTIN is for oral use only. Abuse of OXYCONTIN poses a risk of overdose and death. The risk is increased with concurrent use of OXYCONTIN with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN enhances drug release and increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in OXYCONTIN can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and

valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrence Studies

OXYCONTIN is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OXYCONTIN resulting from a change in formulation, in this section, the original formulation of OXYCONTIN, which is no longer marketed, will be referred to as “original OxyContin” and the reformulated, currently marketed product will be referred to as “OXYCONTIN”.

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OXYCONTIN to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OXYCONTIN relative to an immediate-release oxycodone. When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies

In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OXYCONTIN 30 mg tablets, coarsely crushed OXYCONTIN 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OXYCONTIN, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response (“definitely would not take drug again”) and 100 represents the strongest positive response (“definitely would take drug again”).

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects’ nostrils occurred in 34% (n = 10) of subjects with finely crushed OXYCONTIN, compared with 7% (n = 2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OXYCONTIN was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 5.

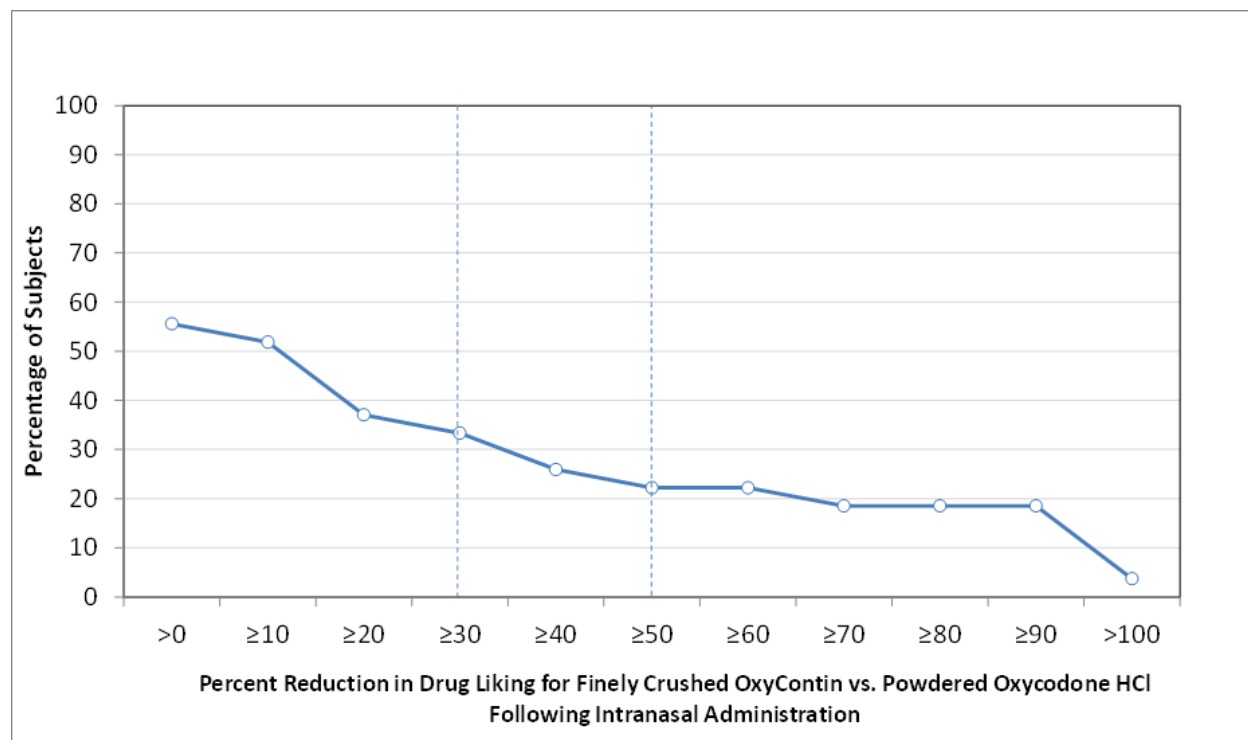
Table 5: Summary of Maximum Drug Liking (E_{\max}) Data Following Intranasal Administration

VAS Scale (100 mm)*		OXYCONTIN (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed OXYCONTIN compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OXYCONTIN vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OXYCONTIN relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OXYCONTIN relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with OXYCONTIN compared to oxycodone HCl, and approximately 22% (n = 6) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for OXYCONTIN vs. oxycodone HCl, N=27 Following Intranasal Administration



The results of a similar analysis of drug liking for finely crushed OXYCONTIN relative to finely crushed original OxyContin were comparable to the results of finely crushed OXYCONTIN relative to powdered oxycodone HCl. Approximately 43% ($n = 12$) of subjects had no reduction in liking with OXYCONTIN relative to original OxyContin. Approximately 57% ($n = 16$) of subjects had some reduction in drug liking, 36% ($n = 10$) of subjects had a reduction of at least 30% in drug liking, and approximately 29% ($n = 8$) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to original OxyContin.

Summary

The *in vitro* data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OXYCONTIN on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OXYCONTIN contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OXYCONTIN can be abused and is

subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)*].

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OXYCONTIN should not be abruptly discontinued [*see Dosage and Administration (2.9)*]. If OXYCONTIN is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see Use in Specific Populations (8.1)*].

10 OVERDOSAGE

Clinical Presentation

Acute overdose with OXYCONTIN can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression

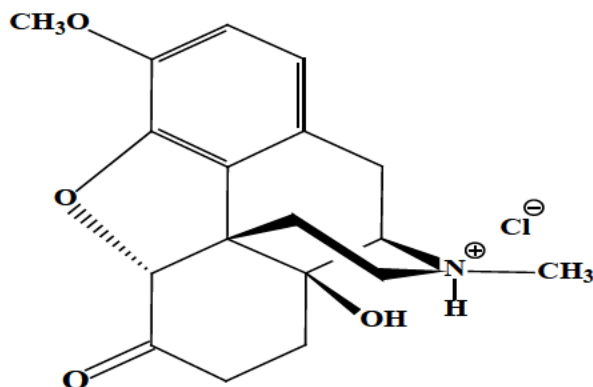
secondary to oxycodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose.

Because the duration of reversal is expected to be less than the duration of action of oxycodone in OXYCONTIN, carefully monitor the patient until spontaneous respiration is reliably reestablished. OXYCONTIN will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

OXYCONTIN® (oxycodone hydrochloride) extended-release tablets is an opioid agonist supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



C₁₈ H₂₁ NO₄ • HCl

MW 351.83

The chemical name is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7).

The 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg tablets contain the following inactive ingredients: butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate, titanium dioxide.

The 10 mg tablets also contain hydroxypropyl cellulose.

The 15 mg tablets also contain black iron oxide, yellow iron oxide, and red iron oxide.

The 20 mg tablets also contain polysorbate 80 and red iron oxide.

The 30 mg tablets also contain polysorbate 80, red iron oxide, yellow iron oxide, and black iron oxide.

The 40 mg tablets also contain polysorbate 80 and yellow iron oxide.

The 60 mg tablets also contain polysorbate 80, red iron oxide and black iron oxide.

The 80 mg tablets also contain hydroxypropyl cellulose, yellow iron oxide and FD&C Blue #2/Indigo Carmine Aluminum Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxycodone is a full opioid agonist and is relatively selective for the mu receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all full opioid agonists, there is no ceiling effect to analgesia for oxycodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in CO₂ tension and electrical stimulation.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [*see Overdosage (10)*].

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Oxycodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [*see Adverse Reactions (6.2)*]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [*see Adverse Reactions (6.2)*].

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration –Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective “drug effect”, analgesia and feelings of relaxation.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [*see Dosage and Administration (2.1, 2.5)*].

Concentration –Adverse Reaction Relationships

There is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [*see Dosage and Administration (2.1, 2.5)*].

12.3 Pharmacokinetics

The activity of OXYCONTIN is primarily due to the parent drug oxycodone. OXYCONTIN is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dissolving OXYCONTIN impairs the controlled-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OXYCONTIN is pH independent. The oral bioavailability of oxycodone is 60% to 87%. The relative oral bioavailability of oxycodone from OXYCONTIN to that from immediate-release oral dosage forms is 100%. Upon repeated dosing with OXYCONTIN in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life ($t_{1/2}$) of oxycodone following the administration of OXYCONTIN was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.

Plasma Oxycodone Concentration over Time

Dose proportionality has been established for OXYCONTIN 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{\max}) and extent of absorption (AUC) (*see Table 6*). Given the short elimination $t_{1/2}$ of oxycodone, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OXYCONTIN. In a study comparing 10 mg of OXYCONTIN every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{\max} , and similar for C_{\min} (trough) concentrations.

TABLE 6

Mean [% coefficient of variation]

Regimen	Dosage Form	AUC (ng·hr/mL)*	C_{\max} (ng/mL)	T_{\max} (hr)
Single Dose†	10 mg	136 [27]	11.5 [27]	5.11 [21]
	15 mg	196 [28]	16.8 [29]	4.59 [19]
	20 mg	248 [25]	22.7 [25]	4.63 [22]
	30 mg	377 [24]	34.6 [21]	4.61 [19]
	40 mg	497 [27]	47.4 [30]	4.40 [22]
	60 mg	705 [22]	64.6 [24]	4.15 [26]
	80 mg	908 [21]	87.1 [29]	4.27 [26]

* for single-dose AUC = AUC_{0-inf}

†data obtained while subjects received naltrexone, which can enhance absorption

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OXYCONTIN.

Distribution

Following intravenous administration, the steady-state volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk [*see Use in Specific Populations (8.4)*].

Elimination

Metabolism

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated *N*-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated *O*-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs [*see Drug Interactions (7)*].

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α - and β -oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Specific Populations

Age: Geriatric Population

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects (age 21-45).

Age: Pediatric Population

In the pediatric age group of 11 years of age and older, systemic exposure of oxycodone is expected to be similar to adults at any given dose of OXYCONTIN.

Sex

Across individual pharmacokinetic studies, average plasma oxycodone concentrations for female subjects were up to 25% higher than for male subjects on a body weight-adjusted basis. The reason for this difference is unknown [see *Use in Specific Populations* (8.9)].

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The mean elimination $t_{1/2}$ for oxycodone increased by 2.3 hours.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in mean elimination $t_{1/2}$ for oxycodone of 1 hour.

Drug Interaction Studies

CYP3A4 Inhibitors

CYP3A4 is the major isoenzyme involved in noroxycodone formation. Co-administration of OXYCONTIN (10 mg single dose) and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and C_{max} by 170% and 100%, respectively [see *Drug Interactions* (7)].

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and C_{max} values by 86% and 63%, respectively [see *Drug Interactions* (7)].

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade has not been shown to be of clinical significance with OXYCONTIN [see *Drug Interactions* (7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of oxycodone have not been conducted.

Mutagenesis

Oxycodone was genotoxic in the in vitro mouse lymphoma assay. Oxycodone was negative when tested at appropriate concentrations in the in vitro chromosomal aberration assay, the in vitro bacterial reverse mutation assay (Ames test), and the in vivo bone marrow micronucleus assay in mice.

Impairment of Fertility

In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg/day). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to Gestation Day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats at any dose tested (up to 8 mg/kg/day), up to 1.3 times a human dose of 60 mg/day.

14 CLINICAL STUDIES

Adult Clinical Study

A double-blind, placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with persistent, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, OXYCONTIN 20 mg, but not 10 mg, was statistically significant in pain reduction compared with placebo.

Pediatric Clinical Study

OXYCONTIN has been evaluated in an open-label clinical trial of 155 opioid-tolerant pediatric patients with moderate to severe chronic pain. The mean duration of therapy was 20.7 days (range 1 to 43 days). The starting total daily doses ranged from 20 mg to 100 mg based on the patient's prior opioid dose. The mean daily dose was 33.30 mg (range 20 to 140 mg/day). In an extension study, 23 of the 155 patients were treated beyond four weeks, including 13 for 28 weeks. Too few patients less than 11 years were enrolled in the clinical trial to provide meaningful safety data in this age group.

16 HOW SUPPLIED/STORAGE AND HANDLING

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 10 mg are film-coated, round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-410-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-410-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 15 mg are film-coated, round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-415-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-415-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 20 mg are film-coated, round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-420-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-420-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 30 mg are film-coated, round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-430-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-430-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 40 mg are film-coated, round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-440-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-440-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 60 mg are film-coated, round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-460-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-460-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 80 mg are film-coated, round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-480-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-480-20**).

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse and Misuse

Inform patients that the use of OXYCONTIN, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [*see Warnings and Precautions (5.1)*]. Instruct patients not to share OXYCONTIN with others and to take steps to protect OXYCONTIN from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting OXYCONTIN or when the dosage is increased, and that it can occur even at recommended dosages [*see Warnings and Precautions (5.3)*]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

To guard against excessive exposure to OXYCONTIN by young children, advise caregivers to strictly adhere to recommended OXYCONTIN dosing.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [*see Warnings and Precautions (5.3)*]. Instruct patients to take steps to store OXYCONTIN securely and to dispose of unused OXYCONTIN by flushing the tablets down the toilet.

Interactions with Benzodiazepines or Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if OXYCONTIN is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [*see Warnings and Precautions (5.6), Drug Interactions (7)*].

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare provider if they are taking, or plan to take serotonergic medications [*see Drug Interactions (7)*].

MAOI Interaction

Inform patients to avoid taking OXYCONTIN while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking OXYCONTIN [see *Drug Interactions (7)*].

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see *Warnings and Precautions (5.8)*].

Important Administration Instructions

Instruct patients how to properly take OXYCONTIN, including the following:

- OXYCONTIN is designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN tablets can result in a fatal overdose [see *Dosage and Administration (2.1)*].
- OXYCONTIN tablets should be taken one tablet at a time [see *Dosage and Administration (2.1)*].
- Do not pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth [see *Dosage and Administration (2.1)*].
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth [see *Dosage and Administration (2.1)*].
- Do not discontinue OXYCONTIN without first discussing the need for a tapering regimen with the prescriber [see *Dosage and Administration (2.9)*].

Hypotension

Inform patients that OXYCONTIN may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see *Warnings and Precautions (5.9)*].

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in OXYCONTIN. Advise patients how to recognize such a reaction and when to seek medical attention [see *Contraindications (4)*, *Adverse Reactions (6)*].

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see *Warnings and Precautions (5.4)*, *Use in Specific Populations (8.1)*].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that OXYCONTIN can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Lactation:

Advise patients that breastfeeding is not recommended during treatment with OXYCONTIN [*see Use in Specific Populations (8.2)*]

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [*see Use in Specific Populations (8.3)*].

Driving or Operating Heavy Machinery

Inform patients that OXYCONTIN may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [*see Warnings and Precautions (5.15)*].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [*see Adverse Reactions (6)*].

Disposal of Unused OXYCONTIN

Advise patients to flush the unused tablets down the toilet when OXYCONTIN is no longer needed.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

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U.S. Patent Numbers 6,488,963; 7,129,248; 8,309,060; 8,808,741; 8,821,929; 8,894,987; 8,894,988; 9,060,976; 9,073,933; 9,492,389, 9,492,391, 9,492,392, 9,492,393, and 9,522,919

Medication Guide

OXYCONTIN® (ox-e-KON-tin) (oxycodone hydrochloride) extended-release tablets, CII

OXYCONTIN is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.
- Not for use in children less than 11 years of age and who are not already using opioid pain medicines regularly to manage pain severe enough to require daily around-the-clock long-term treatment of pain with an opioid.

Important information about OXYCONTIN:

- **Get emergency help right away if you take too much OXYCONTIN (overdose).** When you first start taking OXYCONTIN, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking **OXYCONTIN** with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your OXYCONTIN. They could die from taking it. Store OXYCONTIN away from children and in a safe place to prevent stealing or abuse. Selling or giving away OXYCONTIN is against the law.

Do not take OXYCONTIN if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking OXYCONTIN, tell your healthcare provider if you have a history of:

- head injury, seizures
- problems urinating
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.
- liver, kidney, thyroid problems
- pancreas or gallbladder problems

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of OXYCONTIN during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with OXYCONTIN. It may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking OXYCONTIN with certain other medicines can cause serious side effects that could lead to death.

When taking OXYCONTIN:

- Do not change your dose. Take OXYCONTIN exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 12 hours at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time.
- Swallow OXYCONTIN whole. Do not cut, break, chew, crush, dissolve, snort, or inject OXYCONTIN because this may cause you to overdose and die.
- OXYCONTIN should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth to avoid choking on the tablet.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking OXYCONTIN without talking to your healthcare provider.**
- After you stop taking OXYCONTIN, flush any unused tablets down the toilet.

While taking OXYCONTIN DO NOT:

- Drive or operate heavy machinery until you know how OXYCONTIN affects you. OXYCONTIN can make you sleepy, dizzy, or lightheaded.
- Drink alcohol, or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with OXYCONTIN may cause you to overdose and die.

The possible side effects of OXYCONTIN are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of OXYCONTIN. Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: Purdue Pharma L.P., Stamford, CT 06901-3431, www.purduepharma.com or call 1-888-726-7535

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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OXYCONTIN® II
(OXYCODONE HCl) EXTENDED-RELEASE TABLETS