

## Therapeutic Class Overview

### Opioid Use Disorder Agents

#### INTRODUCTION

##### **Products for Treatment of Opioid Dependence**

- The American Psychiatric Association (APA) defines opioid use disorder as a syndrome characterized by a problematic pattern of opioid use, leading to clinically significant impairment or distress (*APA 2013*).
  - In 2015, approximately 2 million Americans had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin (*American Society of Addiction Medicine [ASAM] 2016*).
- Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence (*Micromedex 2.0 2019*).
  - Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs may dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (Code of Federal Regulations, Title 42, Sec 8).
  - The Drug Addiction Treatment Act of 2000 expanded the clinical context of medication-assisted opioid addiction treatment by allowing qualified physicians to dispense or prescribe specifically approved medications, like buprenorphine, for the treatment of opioid addiction in treatment settings other than the traditional Opioid Treatment Program. In addition, DATA reduced the regulatory burden on physicians who choose to practice opioid addiction therapy by permitting qualified physicians to apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act (*Center for Substance Abuse Treatment 2004*).
  - Naltrexone, an opioid antagonist, is only indicated for the prevention of relapse after opioid detoxification; patients must be opioid-free for at least 7 to 10 days prior to initiation of naltrexone therapy in order to avoid precipitation of withdrawal.
- All buprenorphine products are Schedule III controlled substances (*Drugs @FDA 2019*).
- In 2012, Reckitt Benckiser Pharmaceuticals notified the FDA that they were voluntarily discontinuing production of Suboxone (buprenorphine/naloxone) sublingual tablets as a result of increasing concerns over accidental pediatric exposure with the tablets. The unique child-resistant, unit-dose packaging of the film formulation is believed to be a contributing factor to reduce exposure rates in children. Generic formulations of the sublingual tablets remain available.
- In November 2017, the FDA approved Sublocade (buprenorphine ER) subcutaneous injection for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.
  - Sublocade is injected as a liquid and the subsequent precipitation of the polymer creates a solid depot which contains buprenorphine. Buprenorphine is released via diffusion from, and the biodegradation of, the depot.
- On September 7, 2018, a new dosage strength of buprenorphine/naloxone sublingual films was approved by the FDA under the brand name Cassipa. However, the launch of this product has been delayed pending patent litigation against Dr. Reddy's generic Suboxone film product (see footnotes in Table 1). The current estimated launch date of Cassipa is unknown.
- Lofexidine, an oral central alpha-2 agonist, was approved in May 2018 for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. This product is indicated for short-term use, up to 14 days, during the period of peak opioid withdrawal symptoms.
- Included in this review are the products that are FDA-approved to be used in the treatment of opioid dependence; however, methadone products are not included since they must be dispensed in an opioid treatment program when used for the treatment of opioid addiction in detoxification.
- Medispan Class: Opioid Use Disorder Agents

**Table 1. Medications for Treatment of Opioid Dependence Included Within Class Review**

Drug	Generic Availability
<b>Single Entity Agents</b>	
Lucemyra (lofexidine) tablet	-
naltrexone hydrochloride* tablet	✓
Sublocade (buprenorphine) subcutaneous injection	-
Subutex (buprenorphine)* sublingual tablet	✓
Vivitrol (naltrexone) intramuscular injection	-
<b>Combination Products</b>	
Bunavail (buprenorphine/naloxone) buccal film	-
buprenorphine/naloxone* sublingual tablets	✓
Suboxone (buprenorphine/naloxone) sublingual film	✓ †
Zubsolv (buprenorphine/naloxone) sublingual tablets	- §

\*Brand name product was discontinued; however, generic formulations are available.

†Dr. Reddy, Mylan, and Alvogen received FDA approval for AB-rated generic versions of the Suboxone sublingual film; the launch of these generics was delayed/blocked pending patent litigation against Dr. Reddy. The manufacturer of the branded product, Indivior, launched an authorized generic version (distributed by Sandoz) on February 20, 2019, after the Federal Circuit Court of Appeals issued a decision vacating the primary injunction against Dr. Reddy. Indivior will file an application to the Supreme Court of the United States requesting a stay of the mandate pending resolution of its forthcoming petition for certiorari seeking to overturn the Federal Circuit Courts of Appeals' primary injunction vacatur.

§Generic version not anticipated until 2032.

(Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)

### Products for Emergency Treatment of Opioid Overdose

- Opiate overdose continues to be a major public health problem in the United States (U.S.). It has contributed significantly to accidental deaths among those who use or abuse illicit and prescription opioids. The number of opioid overdoses has risen in recent years, partly due to a nearly 4-fold increase in the use of prescribed opioids for the treatment of pain. Overdose deaths involving opioids increased to more than 42,000 deaths in 2016 (Substance Abuse and Mental Health Services Administration [SAMHSA] 2018).
- Death following opioid overdose can be averted by emergency basic life support and/or the timely administration of an opioid antagonist such as naloxone. As a narcotic antagonist, naloxone displaces opiates from receptor sites in the brain and reverses respiratory depression, which is usually the cause of overdose deaths (SAMHSA 2018, World Health Organization [WHO] 2014).
- Naloxone is provided to patients through the regular course of medical care, by pharmacist-initiated collaborative practice agreements, or through community-based opioid overdose prevention programs (Doe-Simkins 2014).
- Recognizing the potential value of providing naloxone to laypersons, some states have passed laws and changed regulations authorizing prescribers to provide naloxone through standing orders and/or to potential overdose witnesses as well as protecting those who administer naloxone from penalties for practicing medicine without a license (Morbidity and Mortality Weekly Report [MMWR] 2012, Coffin 2018).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (HHS 2018).
- In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression, and hypotension within 1 to 2 minutes after intravenous (IV) administration, 2 to 5 minutes after intramuscular (IM) or subcutaneous (SC) administration, and 8 to 13 minutes after intranasal (IN) administration. Since the half-life of naloxone is much shorter than that of most opioids, repeated administration may be necessary (Lexicomp 2019).
- Naloxone was first approved by the FDA in 1971. In April 2014, an auto-injector formulation of naloxone was approved (Evzio) which incorporates both audio and visual instructions to guide the person administering the drug during a medical emergency. In November 2015, the FDA approved the first IN formulation of naloxone (Narcan nasal spray). Prior to the approval of these products, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (Evzio FDA Summary Review 2014).

Data as of February 19, 2019 LK-U/MG-U/CME

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- Included in this review are the naloxone products that are FDA-approved for opioid overdose.
- Medispan Class: Opioid Antagonists

**Table 2. Medications for Emergency Treatment of Opioid Overdose Included Within Class Review**

Drug	Generic Availability
Evzio (naloxone hydrochloride [HCl]) auto-injector	-
naloxone HCl* injection	✓
Narcan (naloxone HCl) nasal spray	-

\*Brand name product was discontinued; however, generic formulations are available

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

**INDICATIONS**

**Table 3. Food and Drug Administration Approved Indications for Buprenorphine and Buprenorphine/Naloxone Products**

Indication	Single Entity Agent		Combination Products			
	Sublocade (buprenorphine) subcutaneous injection	Subutex (buprenorphine) sublingual tablets	Bunavail (buprenorphine/naloxone) film	buprenorphine/naloxone sublingual tablets	Suboxone (buprenorphine/naloxone) film	Zubsolv (buprenorphine/naloxone) sublingual tablets
Treatment of opioid dependence			✓		✓	✓
Treatment of opioid dependence and is preferred for induction		✓				
Maintenance treatment of opioid dependence				✓		
Treatment of moderate to severe opioid use disorder*	✓					

\*For use in patients who initiated treatment with transmucosal buprenorphine-containing product, followed by dose adjustment for at least 7 days.

(*Prescribing information: buprenorphine sublingual tablets 2018, buprenorphine/naloxone sublingual tablets 2018, Bunavail 2018, Sublocade 2018, Suboxone film 2018, Zubsolv 2018*)

**Table 4. Food and Drug Administration Approved Indications for Naltrexone Agents Used in Opioid Dependence**

Indication	naltrexone hydrochloride tablets	Vivitrol (naltrexone HCl) injection
Blockade of the effects of exogenously administered opioids	✓	
Treatment of alcohol dependence	✓	✓
Prevention of relapse to opioid dependence following opioid detoxification		✓

(*Prescribing information: naltrexone tablets 2017, Vivitrol 2018*)

**Table 5. Food and Drug Administration Approved Indications for Other Agents Used in Opioid Dependence**

Indication	Lucemyra (lofexidine) tablets
Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation	✓

(Prescribing information: Lucemyra 2018)

**Table 6. Food and Drug Administration Approved Indications for Naloxone Products**

Indication	Evzio (naloxone HCl) auto-injector	naloxone HCl injection	Narcan (naloxone HCl) nasal spray
Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system (CNS) depression	✓		✓
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		✓	
Diagnosis of suspected or known acute opioid overdose		✓	
Adjunctive agent to increase blood pressure in the management of septic shock		✓	

(Prescribing information: Evzio 2016, naloxone injection 2015, Narcan nasal spray 2017)

**Limitations of use**

- Prescription of Narcan nasal spray 2 mg should be restricted 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.
- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

**CLINICAL EFFICACY SUMMARY**

**Products for Treatment of Opioid Dependence**

- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Studies have shown that in adult patients with opioid dependence, the percentage of opioid negative urine tests was significantly higher for both buprenorphine and buprenorphine/naloxone compared to placebo, while no significant difference was seen between the 2 active treatment groups (*Daulouede et al 2010, Fudala et al 2003*). In addition, a small randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone (*Strain et al 2011*).
- Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rate or self-reported drug use with longer treatment duration compared to detoxification; however, 1 of the studies showed no significant difference in the percentage of positive urine tests between the 2 treatment groups at 12 weeks (*Kakko et al 2003, Woody et al 2008, Weiss 2011*).

- In a meta-analysis of 21 randomized controlled trials, patients receiving buprenorphine at doses  $\geq 16$  mg/day were more likely to continue treatment compared to patients receiving doses  $< 16$  mg/day; however, no significant difference was seen in the percentage of opioid positive urine tests between the high- and low-dose groups (*Fareed et al 2012*).
- Studies that compared different dosing regimens of buprenorphine showed no difference in rate of treatment retention, percentage of urine tests positive for opioids, or withdrawal symptoms (*Bickel et al 1999, Gibson et al 2008, Petry et al 1999, Schottenfeld et al 2000*).
- One study found that buprenorphine/naloxone sublingual film was comparable to the sublingual tablet form in dose equivalence and clinical outcomes (*Lintzeris et al 2013*).
- A randomized, parallel-group, noninferiority trial (N=758) found that for the treatment of patients with opioid dependence, Zubsolv (buprenorphine/naloxone) sublingual tablets was noninferior to generic buprenorphine sublingual tablets during induction and was noninferior to buprenorphine/naloxone sublingual film during early stabilization (*Gunderson et al 2015*).
- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence (*Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Law et al 2017, Meader et al 2010, Perry et al 2013, Petitjean et al 2001, Soyka et al 2008, Strain et al 2011*). However, when low doses of buprenorphine were studied ( $\leq 8$  mg/day), high doses of methadone ( $\geq 50$  mg/day) proved to be more efficacious (*Farre et al 2002, Ling et al 1996, Mattick et al 2014, Schottenfeld et al 1997*).
- In a 24-week, Phase 3, double blind, placebo-controlled, randomized controlled trial (N=504), the efficacy and safety of multiple subcutaneous injections of buprenorphine (100 mg and 300 mg) over 24 weeks were assessed in treatment-seeking patients with opioid use disorder. Buprenorphine injection was shown to be superior vs placebo in achieving more illicit opioid-free weeks ( $p < 0.0001$ ). The proportion of patients achieving treatment success (defined as any patient with at least 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from week 5 through week 24) was statistically significantly higher in both groups receiving buprenorphine compared to the placebo group (28.4% [300 mg/100 mg], 29.1% [300 mg/300mg], and 2% [placebo]) ( $p < 0.0001$ ) (*FDA Advisory Committee Briefing Document, Sublocade Prescribing Information*).
- Extended-release intramuscular naltrexone was compared to buprenorphine/naloxone sublingual film in a 24-week, open-label, randomized controlled trial (N=570). More induction failures were seen with extended-release intramuscular naltrexone; as a result, in the intention-to-treat analysis, relapse-free survival was lower with extended-release intramuscular naltrexone compared to sublingual buprenorphine/naloxone. However, among patients who were able to successfully initiate treatment, extended-release intramuscular naltrexone had similar efficacy to buprenorphine/naloxone in terms of relapse prevention (*Lee et al 2018*). A 12-week, randomized, open-label, noninferiority trial (N=159) similarly found that extended-release intramuscular naltrexone was noninferior to oral buprenorphine/naloxone in terms of negative urine drug tests and days of opioid use (*Tanum et al 2017*).
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*).
- The safety and efficacy of lofexidine for inpatient treatment of opioid withdrawal symptoms was examined in an 8-day, randomized, double-blind, placebo-controlled trial (N=264). In this study, patients treated with lofexidine had lower scores on the Short Opioid Withdrawal Scale (SOWS) Gossop scale on day 3 compared to placebo. More patients in the placebo group terminated study participation early (*Gorodetzky et al 2017*). Similar results were found in another, unpublished trial (*Lucemyra prescribing information 2018*). Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion (*Gowing et al 2016, Gowing et al 2017*). It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).

### **Products for Emergency Treatment of Opioid Overdose**

- The approval of Evzio auto-injector and Narcan nasal spray were based on pharmacokinetic bioequivalence studies comparing these products to a generic naloxone product, delivered SC or IM. No clinical studies were required by the FDA (*Prescribing information: Evzio 2016, Narcan 2017*).

- The manufacturers also conducted a human factors validation study in which participants were asked to deliver a simulated dose of the drug to a mannequin without training and most demonstrated appropriate use of the device (*FDA Summary Review: Evzio 2014, Narcan nasal spray 2015*).
- Studies have suggested that IN naloxone is an effective option in the treatment of opioid overdose (*Kelly et al 2005, Kerr et al 2009, Merlin et al 2010, Robertson et al 2009, Sabzghabaee et al 2014*).
- A meta-analysis of naloxone studies found that lay administration of naloxone was associated with significantly increased odds of recovery compared with no naloxone administration (odds ratio: 8.58, 95% confidence interval [CI], 3.90 to 13.25) (*Giglio et al 2015*).
- A 2-year, non-randomized intervention study found that prescription of naloxone to patients who were prescribed long-term opioids for chronic pain was associated with a 47% decrease in opioid-related emergency visits per month after 6 months and a 63% decrease after 1 year compared to those who did not receive naloxone (*Coffin et al 2016*).

## CLINICAL GUIDELINES

- The American Academy of Pediatrics (AAP), APA, American Society of Addiction Medicine (ASAM), Center for Substance Abuse Treatment (CSAT)/United States Substance Abuse and Mental Health Services Administration (SAMHSA), and the Veterans Health Administration (VHA) have published guidelines for the treatment of opioid dependence. In general, these guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman 2015, Kleber et al 2006, Kraus et al 2011, SAMHSA 2018, VHA 2015*).
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications (*Kampman 2015, VHA 2015*).
  - Using tapering doses of opioid agonists has been shown to be superior to alpha-2 adrenergic agonists in terms of retention and opioid abstinence. However, the use of non-opioid medications may be the only option available to clinicians in some healthcare settings and may also facilitate the transition of patients to opioid antagonist medications (eg, naltrexone) and help prevent subsequent relapse.
- Various organizations including the World Health Organization (WHO) and the ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Kampman 2015*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

## SAFETY SUMMARY

### Products for Treatment of Opioid Dependence

- Buprenorphine and buprenorphine/naloxone products are contraindicated in patients with known hypersensitivity to the active ingredients.
- Buprenorphine products have several warnings and precautions, including: abuse potential; respiratory depression; CNS depression; unintentional pediatric exposure; neonatal opioid withdrawal; adrenal insufficiency; risk of opioid withdrawal with abrupt discontinuation of treatment; hepatitis and hepatic events; hypersensitivity reactions; precipitation of opioid withdrawal signs and symptoms; use in patients with impaired hepatic function; impairment of ability to drive or operate machinery; orthostatic hypotension; elevation of cerebrospinal fluid pressure; elevation of intracholedochal pressure; and effects in acute abdominal conditions
- Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk for adverse events, including overdose, respiratory depression, and death. Cessation of benzodiazepines or other CNS depressants

is preferred in most cases of concomitant use. This additional warning was added to opioid products in February 2018 after data demonstrated an increased risk of mortality in patients receiving benzodiazepines while on opioid maintenance treatment (*Abrahamsson et al 2017, FDA Drug Safety Communication 2017*).

- The buprenorphine subcutaneous injection also has several unique warnings and precautions, including: serious harm or death could result if administered IV (boxed warning); risks associated with treatment of emergent acute pain; use in patients at risk for arrhythmia.
- In the treatment of addiction involving opioid use in pregnant women, the buprenorphine/naloxone combination product is not recommended for use (insufficient evidence); however, the buprenorphine monoproduct is a reasonable and recommended option for use.
- Similar to other opiate products, these products may increase intracholedochal pressure, increase cerebrospinal fluid pressure, and obscure diagnosis or exacerbate acute abdominal symptoms.
- These products should not be used as analgesics.
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome.
- All of the buprenorphine-containing products have an associated risk evaluation and mitigation strategy (REMS) program (*REMS@FDA 2019*).
- Lofexidine has several warnings and precautions, including: risk of hypotension, bradycardia, and syncope; risk of QT prolongation; increased risk of CNS depression with concomitant use of CNS depressant drugs; and increased risk of opioid overdose in patients who complete opioid discontinuation and resume opioid use.
- Sudden discontinuation of lofexidine can cause a marked rise in blood pressure and symptoms that include diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain. Lofexidine should be discontinued by gradually reducing the dose.
- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
- The safety of lofexidine in pregnancy has not been established.
- Naltrexone products are contraindicated in: patients receiving opioid analgesics; patients currently dependent on opioids (including those currently maintained on opioid agonists); patients in acute opioid withdrawal; individuals who have failed a naloxone challenge test or have a positive urine screen for opioids; individuals with a history of sensitivity to naltrexone or other components of the product; and individuals with acute hepatitis or liver failure (oral naltrexone only). Extended-release injectable naltrexone is contraindicated in patients with hypersensitivity to polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of the diluent.
- Naltrexone can precipitate withdrawal if given to an opioid-dependent patient. Prior to initiating naltrexone, an opioid-free interval of 7 to 10 days is recommended for patients previously dependent on short-acting opioids; patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for up to 2 weeks. A naloxone challenge test may be helpful to determine whether or not the patient has had a sufficient opioid-free period prior to initiating naltrexone.
- Patients may be more vulnerable to opioid overdose after discontinuation of naltrexone due to decreased opioid tolerance.
- Monitor patients on naltrexone for the development of depression or suicidality.
- Warnings unique to extended-release intramuscular naltrexone include: injection site reactions, which may be severe; eosinophilic pneumonia; hypersensitivity reactions, including anaphylaxis; use in patients with thrombocytopenia or any coagulation disorder; and interference with certain immunoassay methods of urine opioid detection.
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release intramuscular naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.
- There are no adequate and well-controlled studies of naltrexone in pregnant women; it should be used only if the potential benefit justifies the potential risk to the fetus.
- Extended-release intramuscular naltrexone has a REMS program due to the risk of severe injection site reactions (*REMS@FDA 2019*).

### **Products for Emergency Treatment of Opioid Overdose**

- These products are contraindicated in patients with hypersensitivity to naloxone or to any of the other ingredients.

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- These products carry warnings and precautions for risks of recurrent respiratory and CNS depression, limited efficacy with partial agonists or mixed agonists/antagonists (eg, buprenorphine, pentazocine), and precipitation of severe opioid withdrawal.
- Naloxone may precipitate acute withdrawal symptoms in opioid-dependent patients including anxiety, tachycardia, sweating, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, increased blood pressure, and abdominal or muscle cramps. Opioid withdrawal signs and symptoms in neonates also include convulsions, excessive crying, and hyperactive reflexes.

**DOSING AND ADMINISTRATION**

**Table 7a. Dosing and Administration for Products for Treatment of Opioid Dependence**

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
<b>Single Entity Agents</b>				
Lucemyra (lofexidine)	Tablet	Oral	Four times daily at 5- to 6-hour intervals	<ul style="list-style-type: none"> <li>• May be continued for up to 14 days with dosing guided by symptoms</li> <li>• Adjust dose for patients with hepatic or renal impairment</li> </ul>
Naltrexone hydrochloride	Tablet	Oral	Single daily dose  May also be dosed every other day or every 3 days	<ul style="list-style-type: none"> <li>• Contraindicated in patients with acute hepatitis or liver failure</li> <li>• Use caution in patients with hepatic or renal impairment</li> </ul>
Sublocade (buprenorphine)	Subcutaneous injection	SC	Monthly (minimum 26 days between doses)	<ul style="list-style-type: none"> <li>• Can only be administered by a healthcare provider</li> <li>• Patients with moderate or severe hepatic impairment are not candidates for this product</li> </ul>
Subutex (buprenorphine)	Sublingual tablets	Oral	Single daily dose	<ul style="list-style-type: none"> <li>• Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half and monitor for signs and symptoms of toxicity or overdose.</li> </ul>
Vivitrol (naltrexone extended-release)	Intramuscular injection	IM	Monthly or every 4 weeks	<ul style="list-style-type: none"> <li>• Can only be administered by a healthcare provider</li> <li>• Use caution in patients with moderate to severe renal impairment</li> </ul>
<b>Combination Products</b>				
Bunavail, Suboxone, Zubsolv (buprenorphine/naloxone)	Buccal film (Bunavail)  Sublingual film (Suboxone)  Sublingual tablet (Zubsolv; generics equivalent to Suboxone tablet)	Oral	Bunavail: Single daily dose (except day 1 of induction for patients dependent on heroin or other short-acting opioid products: start with an initial dose of 2.1 mg/0.3 mg and repeat at approximately 2 hours, under supervision, to a total dose of 4.2 mg/0.7 mg based on the control of acute withdrawal symptoms)  Suboxone: Single daily dose (except day 1 of induction: titrate in	<ul style="list-style-type: none"> <li>• These products should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.</li> </ul>



Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			<p>buprenorphine 2 mg to 4 mg increments at approximately 2 hour intervals based on the control of acute symptoms)</p> <p>Sublingual tablet generics (Suboxone): Single daily dose</p> <p>Zubsolv: Single daily dose (except day 1 of induction: divided into doses of 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2 hour intervals)</p>	

See the current prescribing information for full details

**Table 7b. Equivalent Doses of Buprenorphine/Naloxone Combination Products\***

Bunavail buccal film	buprenorphine/naloxone sublingual tablets and/or Suboxone sublingual film	Zubsolv sublingual tablets
-	2 mg/0.5 mg	1.4 mg/0.36 mg
2.1 mg/ 0.3 mg	4 mg/1 mg	2.9 mg/0.71 mg
4.2 mg/ 0.7 mg	8 mg/2 mg	5.7 mg/1.4 mg
6.3 mg/1 mg	12 mg/3 mg	8.6 mg/2.1 mg
	16 mg/4 mg	11.4 mg/2.9 mg

\*Systemic exposures of buprenorphine and naloxone may differ when patients are switched from tablets to films or vice versa.

**Table 8. Dosing and Administration for Products for Emergency Treatment of Opioid Overdose**

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evzio (naloxone HCl)	Auto-injector	IM/SC	<ul style="list-style-type: none"> <li>After initial dose, additional doses should be administered, using a new device, if the patient does not respond or responds and then relapses into respiratory depression.</li> <li>Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.</li> </ul>	<ul style="list-style-type: none"> <li>The requirement for repeat doses depends upon the amount, type, and route of administration of the opioid being antagonized.</li> </ul>
Naloxone HCl	Vials, prefilled syringe, solution cartridge	IV	<p><i>Adults:</i></p> <ul style="list-style-type: none"> <li>An initial dose may be administered IV. It may be repeated at 2 to 3 minute intervals if the desired degree of counteraction and improvement in respiratory functions are not obtained.</li> </ul> <p><i>Children:</i></p> <ul style="list-style-type: none"> <li>The usual initial dose in</li> </ul>	<ul style="list-style-type: none"> <li>IM or SC administration may be necessary if the IV route is not available.</li> <li>The American Academy of Pediatrics, however, does not endorse SC or IM administration in opiate intoxication since absorption may be erratic or delayed.</li> </ul>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			children is given IV; a subsequent dose may be administered if the desired degree of clinical improvement is not obtained.	
Narcan (naloxone HCl)	Nasal spray	Intranasal	<ul style="list-style-type: none"> <li>• A single spray should be administered into 1 nostril.</li> <li>• Additional doses should be administered, using a new nasal spray device in alternating nostrils, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.</li> </ul>	

See the current prescribing information for full details

## CONCLUSION

### Products for Treatment of Opioid Dependence

- Buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, Bunavail (buprenorphine/naloxone) buccal film, Sublocade (buprenorphine) subcutaneous injection, Suboxone (buprenorphine/naloxone) sublingual film, and Zubsolv (buprenorphine/naloxone) sublingual tablets are used for the treatment of opioid dependence. Some products are indicated for maintenance treatment only, while others are indicated for both induction and maintenance.
- Buprenorphine is suggested as a first-line maintenance treatment for opioid use disorder; it may be preferred over methadone because it is safer and does not require clinic-based treatment. Buprenorphine is typically administered in a combination product with naloxone, an opioid antagonist, to discourage abuse. These agents are Schedule III controlled substances (*Strain 2018*).
- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Physicians prescribing buprenorphine for opioid dependency must undergo specialized training due to the potential for abuse and diversion. Because of these risks, buprenorphine monotherapy should be reserved for patients who are pregnant or have a documented allergy to naloxone (*DATA 2000, CSAT 2004*).
- Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence (*Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Meader et al 2010, Petitjean et al 2001, Soyka et al 2008, Mattick et al 2014, Strain et al 2011*).
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome. These products also have REMS criteria.
- Lofexidine is an oral central alpha-2 agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation.
- Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion (*Gowing et al 2016, Gowing et al 2017*). It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).
- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.

- Naltrexone is an opioid antagonist. Oral naltrexone is indicated for the treatment of alcohol dependence and blockade of the effects of exogenously administered opioids. Extended-release intramuscular naltrexone is indicated for the treatment of alcohol dependence and the prevention of relapse to opioid dependence following opioid detoxification. In order to initiate naltrexone treatment, patients must be opioid-free for at least 7 to 10 days to avoid precipitation of withdrawal.
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). Extended-release intramuscular naltrexone has been shown to have similar efficacy to oral buprenorphine/naloxone among patients who are able to successfully initiate treatment (*Lee et al 2018, Tanum et al 2017*).
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release intramuscular naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Extended-release intramuscular naltrexone also has a REMS program.
- The AAP, APA, ASAM, CSAT/SAMHSA, and VHA publish guidelines for the treatment of opioid dependence. These guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman et al 2015, Kleber et al 2006, Kraus et al 2011, VHA 2015*).
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications. Lofexidine has not been added to practice guidelines but it likely has a similar place in therapy as clonidine (*Kampman 2015, VHA 2015*).

### **Products for Emergency Treatment of Opioid Overdose**

- Naloxone is the standard of care to treat opioid overdose. It has been used by medical personnel for over 40 years and its use outside of the medical setting has gained traction through improvements in legislation and community-based opioid overdose prevention programs.
- Evzio (naloxone HCl) auto-injector, naloxone HCl injection, and Narcan (naloxone HCl) nasal spray are approved for treatment of known or suspected opioid overdose. Prior to the approval of Evzio and Narcan nasal spray, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).
- Naloxone can be administered IV, IM, or SC using naloxone vials/syringes as well as IM or SC using an auto-injector device (Evzio). Although Narcan nasal spray is the first IN formulation to be FDA-approved, naloxone has historically been given IN off-label via kits containing a syringe and an atomization device. Potential advantages of IN administration of naloxone include easier disposal, no needle stick risk, and avoidance of needle anxiety. Both Evzio and Narcan nasal spray are designed for use by laypersons.
- The approval of Evzio and Narcan nasal spray were based on pharmacokinetic bioequivalence studies. No new clinical studies were required by the FDA.
- Various organizations including WHO and ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Kampman 2015*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

- The U.S. HHS has recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 MME per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (HHS 2018).

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