

Drug Class Update with New Drug Evaluation: Substance Use Disorders

Date of Review: January 2019

Generic Name: Lofexidine

End Date of Literature Search: 8/10/2018

Brand Name (Manufacturer): Lucemyra™ (US World Meds)

Dossier Received: Yes

Current Status of PDL Class: See **Appendix 1**.

Purpose for Class Update:

Review new published data for management of substance use disorders to help inform whether current Oregon Health Plan (OHP) policies remain appropriate for access to these medications. To review evidence for a new alpha2-adrenergic agonist, lofexidine, recently approved by the United States (U.S.) Food and Drug Administration (FDA) for short term mitigation of withdrawal symptoms after abrupt discontinuation of short-acting opioids.

Research Questions:

1. Is there new evidence for differences in efficacy or harms between drug therapies for substance use disorder (SUD)?
2. Are there subpopulations based on demographics (i.e., adolescents, elderly, pregnant women) in which a drug for SUD may be more effective or less harmful than other drugs?
3. What is evidence for the safety and efficacy for lofexidine to mitigate withdrawal symptoms from opioid discontinuation?

Conclusions:

CLASS REVIEW:

- Since the last review, the following new evidence has been identified for management of SUD: 3 systematic reviews and meta-analyses,¹⁻³ 1 randomized controlled trial (RCT),⁴ and 1 clinical practice guideline.⁵ In addition, 1 new formulation,⁶ and 1 new indication has been approved.⁷ Due to the opioid epidemic, most of recent evidence is focused on management of opiate use disorder (OUD) with a focus on withdrawal symptoms and completion of withdrawal treatment. There is insufficient data to assess long term outcomes such as relapse rates and sustained abstinence.
- A high quality systematic review evaluated evidence on safety and efficacy of alpha2-adrenergic agonists (lofexidine and clonidine) in managing the acute phase of opioid withdrawal. Moderate quality evidence from three studies comparing alpha2-adrenergic agonists and placebo showed completion of withdrawal treatment was significantly more likely with an adrenergic agonist (Risk Ratio (RR) 1.95; 95% confidence interval (CI) 1.34 to 2.84) and severe withdrawal was significantly less likely with an adrenergic agonist (RR 0.32; 95% CI 0.18 to 0.57).² For the comparison of alpha2-adrenergic agonists with tapering doses of methadone, moderate quality evidence suggests there is no significant difference in severity of the withdrawal episode (Standardized Mean Difference (SMD) 0.13; 95%CI -0.24 to 0.49).² Moderate quality evidence also shows no significant differences were observed in incidence of adverse

events (RR 2.02; 95% CI 0.62 to 6.64; 203 participants) or completion rates of withdrawal treatment (RR 0.91; 95% CI 0.75 to 1.11; 8 trials; 489 participants) for the adrenergic agonists versus methadone comparisons.²

- A moderate quality systematic review and meta-analysis assessed comparative evidence for the use of buprenorphine in management of opioid withdrawal.¹ The included trials compared buprenorphine to clonidine, lofexidine, and methadone or different buprenorphine dosing regimens.¹ A meta-analysis of 5 moderate quality trials supports a conclusion of no difference between buprenorphine and methadone for withdrawal completion rates (RR 1.04; 95% CI 0.91 to 1.20; N=457).¹ Relative to clonidine or lofexidine, buprenorphine was associated with a lower average withdrawal score (indicating less severe withdrawal) during the treatment episode with an effect size that is considered to be small to moderate (SMD -0.43; 95% CI -0.58 to -0.28; N = 902; studies = 7; moderate quality).¹ Patients receiving buprenorphine stayed in treatment more days than adrenergic agonists (mean days in treatment with buprenorphine ranged from 25% to 97%; mean days in treatment with adrenergic agonists ranged from 21% to 70%; SMD 0.92, 95% CI 0.57 to 1.27; N=558; studies=5; moderate quality) and were more likely to complete withdrawal treatment (RR 1.59, 95% CI 1.23 to 2.06; N=1264; studies=12; moderate quality).¹ The authors did not report absolute risk reduction for these outcomes.
- In 2017 the Canadian Agency for Drugs and Technologies in Health (CADTH) published a rapid response report to evaluate the comparative effectiveness of monotherapy buprenorphine and buprenorphine-naloxone formulations (e.g., sublingual films, sublingual tablets, implants) for treatment of OUD.³ Of the 5 RCTs which met inclusion criteria, all but two were industry-sponsored and there were limitations with respect to study design (e.g., non-inferiority, open-label), clinically relevant outcomes and treatment duration.³ All the buprenorphine formulations examined in the selected studies showed a similar clinical response in patients with OUD, with significantly higher rates of abuse, misuse and diversion found in sublingual buprenorphine-naloxone tablet formulations compared to the film preparations.³ The use of buprenorphine implants was associated with high rates of treatment retention.³ The rates of adverse effects were low among buprenorphine formulations with no significant differences observed.³ The findings indicate that the use of newer buprenorphine formulations may be safe to use in this population, but the included trials were relatively short in duration and may have been underpowered to detect rarer adverse effects.³
- The Canadian Research Initiative in Substance Misuse (CRISM) developed a national guideline for treatment of OUD.⁵ Using the AGREE-II instrument, the guidelines were appraised as having high methodological quality.⁸ Key recommendations for first and second-line OUD treatments in adults based on high quality evidence include:
 - While shown to be essentially as efficacious as methadone in clinical trials, buprenorphine–naloxone has several safety advantages over methadone, including a reduced risk of fatal overdose because of its lower potential for respiratory depression.⁵ Given the superior safety profile of buprenorphine–naloxone and its potential for flexible take-home dosing in comparison to other opioid agonist medications, initiate opioid agonist treatment (with buprenorphine–naloxone whenever feasible), to reduce the risk of toxicity, morbidity and death, and to facilitate safer take-home dosing (strong recommendation).⁵
 - For individuals responding poorly to buprenorphine–naloxone, consider transition to methadone treatment (strong recommendation).⁵
 - Initiate opioid agonist treatment with methadone when treatment with buprenorphine–naloxone is not the preferred option such as those individuals with a high opioid tolerance, severe opioid withdrawal symptoms or those requiring supervised administration due to poor adherence (strong recommendation).⁵
- The FDA approved buprenorphine extended-release injection (Sublocade™) to treat patients with moderate-to-severe OUD who have first received treatment with a transmucosal buprenorphine-containing product for at least 7 days.⁶ Buprenorphine extended-release injection is a 100 or 300 mg subcutaneous injection administered once a month by a health care professional (HCP).⁶
- In April 2017, Bunavail® (buprenorphine and naloxone) buccal film received expanded approval to use this formulation during the induction phase of treatment for patients dependent on heroin or short-acting opioid products.⁷ The previous approved dosing for Bunavail® only addressed the maintenance phase of treatment.⁷

- No sub-group analyses were available for data specific to Medicaid patients or specific populations (e.g., pregnant women, incarcerated individuals, adolescents, or elderly patients).

LOFEXIDINE NEW DRUG EVALUATION

- There is poor quality evidence from one published trial that adults undergoing acute withdrawal from opioids or heroin experienced less symptoms with lofexidine compared to placebo as assessed by the mean Short Opioid Withdrawal Scale (SOWS)-Gossop on day 3 of treatment.⁹ For this trial, the investigators assumed a minimal clinically significant difference of 5 points.⁹ The mean SOWS-Gossop scores on day 3 were 8.67 and 6.32 for placebo and lofexidine, respectively, which demonstrated a significant statistical difference between the 2 arms (least squares mean difference (LSMD) = -2.24, 95% CI -3.88 to -0.6; $p=0.009$).⁹ However, this difference did not meet the pre-specified clinical significance of a 5 point difference.
- Comparison of time-to-dropout between placebo and lofexidine was selected as a co-primary endpoint by the investigators.⁹ Each study day was divided into four 6 hour time quadrants (i.e., 6am–12pm; 12pm–6pm; 6pm–12am; and, 12am–6am) and time-to-dropout was measured as the number of 6 hour time quadrants until withdrawal during the 5-day treatment phase.⁹ Poor quality evidence showed that early termination was statistically higher in the placebo group compared to lofexidine as assessed by the mean number of time quadrants (6.4 vs. 6.9 respectively; $p=0.0034$).⁹ However, the calculated difference was 0.5 time quadrants, or 3 hours, which is not a clinically significant difference in time to withdrawal.
- Moderate quality evidence showed early termination of opioid withdrawal treatment was significantly more common in the placebo group compared to lofexidine (61% versus 44% of subjects, respectively).⁹
- In clinical trials the most common adverse reactions that occurred with lofexidine in 10% or more of subjects compared to placebo, were orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth during 5 to 7 days of treatment.¹⁰ Rates of serious and severe adverse effects requiring treatment discontinuation were relatively low.
- There is insufficient data to evaluate the efficacy of lofexidine to other treatment options such as clonidine.

Recommendations:

- Make lofexidine non-preferred on the Prioritized Drug List (PDL) and implement PA criteria to ensure appropriate utilization (**Appendix 5**).
- Add extended release subcutaneous buprenorphine injection (Sublocade™) to PA criteria for buprenorphine and buprenorphine/naloxone products (**Appendix 6**).
- Evaluate comparative drug costs in executive session.

Summary of Prior Reviews and Current Policy

Treatment for SUD was last reviewed by the Pharmacy and Therapeutics Committee in September 2016. High quality evidence was identified for use of acamprosate and oral naltrexone to decrease alcohol consumption in patients with alcohol use disorder when used concurrently with psychosocial interventions; however, there is insufficient evidence to support their use based on an improvement in clinically relevant health outcomes (i.e., morbidity or mortality) alone.¹¹ The 2014 clinical practice guideline from the Veterans Affairs and Department of Defense (VA/DoD) for the management of substance abuse disorders strongly recommends that treatment choice between acamprosate, disulfiram, naltrexone (oral or extended-release injection) or topiramate be individualized based on specific needs and patient preferences.¹² In all cases, strong psychosocial interventions are needed to successfully treat patients with alcohol use disorder.¹²

For patients with a diagnosis of OUD, the VA/DoD guideline strongly recommends buprenorphine/naloxone or methadone in an Opioid Treatment Program (OTP) depending on specific patient needs or preferences.¹² An OTP is an accredited program with Substance Abuse and Mental Health Services Administration (SAMHSA) certification and Drug Enforcement Administration (DEA) registration in which providers may administer and dispense medications FDA-approved to treat opioid addiction including methadone and buprenorphine.¹³ Alternatively, buprenorphine without naloxone is strongly recommended to be used in patients who are pregnant, and extended-release injectable naloxone is recommended as an option for patients for whom buprenorphine/naloxone or methadone is contraindicated, unacceptable, or unavailable, and who have established opioid abstinence for a sufficient period of time.¹⁴ In all cases, strong psychosocial interventions are needed to successfully treat patients with opioid use disorder. Otherwise, there is insufficient evidence to know with certainty whether buprenorphine products are more effective or safer when given in designated OTP or in private physician offices, or whether daily supplies should be administered or multi-day supplies may be administered.

In the Oregon Health Plan (OHP) Fee-For-Service (FFS) program, preferred agents on the Preferred Drug List (PDL) include: buprenorphine/naloxone film and sublingual tablets, acamprosate tablets, naltrexone extended-release injection, and naltrexone tablets. **Appendix 1** lists the current PDL status for medications used in treatment of SUD. Buprenorphine sublingual tablets are restricted for use in pregnant females and all buprenorphine monotherapy products require prior authorization (PA) as outlined in the clinical PA criteria listed in **Appendix 6**. In the first quarter of 2018 (January 2018 through April 2018), 75% of OHP FFS claims for SUD medications were for buprenorphine/naloxone, 22% of claims were for naltrexone, and 3% of claims were for acamprosate.

Background:

Substance use disorders can develop in individuals who use tobacco, alcohol, opioids, or other addicting drugs in harmful quantities.¹² The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) specifically recognizes SUDs related to substances such as tobacco, alcohol, opioids, cannabis, sedatives, and anxiolytics.¹⁵ According to the DSM-V, SUDs are associated with a pattern of inappropriate substance use that adversely affects one's personal or professional life or results in noticeable distress.¹⁵ Opioid use disorder is the diagnostic term used for a chronic neurobiological disease characterized by a problematic pattern of opioid use leading to significant impairment or distress and includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, the opioid is used in doses far greater than the amount needed for treatment of that medical condition.¹⁶

In 2016, over 63,000 persons died of a drug overdose in the United States; 66% involved an opioid.¹⁷ In July 2018, the Center for Disease Control (CDC) issued an update to alert health care providers about new developments in the opioid epidemic related to increasing trends of overdoses and deaths due to synthetic opioids related to fentanyl and fentanyl analogs.¹⁸ The CDC guidance states multiple dosages of naloxone may need to be administered per overdose event because of fentanyl and fentanyl analog's increased potency relative to other opioids.¹⁸ A recently published study characterizes trends for synthetic opioid involvement (primarily illicit fentanyl) in drug overdose deaths using 2010-2016 mortality data.¹⁹ In 2016, synthetic opioids eclipsed prescription opioids as the most common drug involved in overdose deaths in the United States.¹⁹ The researchers found that 46% of the 42,249 opioid-related overdose deaths in 2016 involved synthetic opioids, up from 14% of 21,089 opioid-related deaths in 2010 ($p < 0.01$).¹⁹ Of 42,249 opioid-related overdose deaths in 2016, synthetic opioids were involved in 19,413 deaths, prescription opioids in 17,087 deaths, and heroin in 15,469 deaths.¹⁹ In August 2018, the CDC issued an additional alert regarding increasing trends in OUD observed in pregnant women.²⁰ Nationally, the prevalence of opioid use disorder in pregnant women more than quadrupled during 1999–2014 (from 1.5 per 1,000 delivery hospitalizations to 6.5; $p < 0.05$).²⁰ According to the CDC, continued national, state, and provider efforts to prevent, monitor, and treat opioid use disorder among reproductive-aged and pregnant women are needed.²⁰

Medication-assisted treatment (MAT) is a comprehensive approach that combines approved medications with counseling and other behavioral therapies to treat SUDs associated with alcohol, tobacco and opioids. Methadone, buprenorphine, or naltrexone are the 3 FDA-approved medications used to manage OUD. For treatment of OUD, methadone can only be administered at a SAMHSA-certified OTP.¹³ Buprenorphine can be prescribed and administered in a primary care setting by physicians, physician’s assistants, and nurse practitioners with a Drug Addiction Treatment Act (DATA) waiver.¹³ Naltrexone is not subject to these federal regulations.¹³ The long acting injectable formulation of naltrexone can be given in both general healthcare and specialty substance use disorder treatment settings. According to the VA/DoD guidelines, there is insufficient evidence at this time to recommend oral naltrexone because it requires a highly motivated patient to be successful and it has not consistently demonstrated superiority to control groups at treatment retention or in opioid consumption.¹² Patients who initiate naltrexone treatment must be free of opioid dependence (i.e., greater than 7 days without acute withdrawal symptoms).¹⁶

Buprenorphine, a partial opioid agonist, was originally FDA approved as an immediate release injection administered every six to eight hours to manage acute pain.²¹ The daily buccal film and weekly transdermal patch formulations of buprenorphine are FDA-approved to manage chronic pain, but not OUD.²¹ In 2016, the U.S. Food and Drug Administration (FDA) approved Probuphine®, a monotherapy buprenorphine product administered via subdermal implant for management of OUD.²² The implant embeds buprenorphine in four matchstick-size rods in a patient’s upper arm that release medication over a 6 month period.²² The buprenorphine implant is designed only for patients who have received buprenorphine/naloxone maintenance therapy for at least 3 months.²² In November 2017, the FDA approved Sublocade™ a once-monthly buprenorphine extended-release subcutaneous injection for management of OUD.⁶ Sublocade™ uses a proprietary delivery system that induces the drug to form a solid deposit inside the patient, gradually biodegrading to an active therapeutic agent.⁶ The FDA approved this product using priority and fast track pathways due to the dramatic increase in people diagnosed with OUD requiring treatment.⁶ The safety and efficacy of Sublocade™ were evaluated in two clinical studies in adults with a diagnosis of moderate-to-severe OUD who began treatment with buprenorphine/naloxone sublingual film for at least 7 days before transitioning to the extended-release subcutaneous injection.⁶

The combination of buprenorphine and naloxone was FDA approved as an indication for OUD in 2002.²³ Co-formulation of buprenorphine with naloxone reduces the risk of diversion and non-medical use compared to monotherapy preparations. The naloxone component exerts no antagonist effect when taken sublingually as directed, but can precipitate withdrawal symptoms in opioid-tolerant individuals if injected.⁵ The once daily buprenorphine/naloxone combinations are available in a variety of doses and formulations including sublingual tablets, buccal film, and sublingual film. **Table 1** provides an overview of the 4 medications FDA-approved to manage opioid withdrawal and dependence in patients with OUD.

Table 1. Comparison of medication-assisted treatment options for moderate-to-severe opioid use disorder²⁴

	Methadone	Naltrexone	Buprenorphine/Naloxone	Buprenorphine
Mechanism of Action at mu-Opioid Receptor	Agonist	Antagonist	Partial Agonist/Antagonist	Partial Agonist
DEA Schedule	Schedule II	Legend Drug	Schedule III	Schedule III
Phase of Treatment	-Medically supervised withdrawal -Maintenance of opioid dependence	-Prevention of relapse to opioid dependence, following medically supervised withdrawal	-Treatment of opioid dependence	-Treatment of opioid dependence in stable patients initiated on buprenorphine/naloxone therapy for at least 7 days (Sublocade™) or 3 months (Probuphine®).

Setting	Administered at SAMHSA-certified OTP	Tablets provided as take-home medication. Monthly injection requires administration by a health care provider.	Prescribing restricted to a health care provider with DATA waiver. Can be provided as take-home medication.	-Prescribing and administration restricted to a health care provider with DATA waiver. -Providers who insert/remove inserts must obtain special live training and be certified through Probuphine® REMS program. -Sublocade™ can only be dispensed and administered by pharmacies and health care providers that have enrolled in REMS program and are certified to dispense/purchase. Prescriber offices that only order Sublocade® from a certified pharmacy for a specific patient are exempt from certification.
Brand Name and Formulation	Dolophine®: Oral Tablets Intensol™, Methadose™: Oral Concentrate Diskets®: Dispersible Tablets	Generic: Oral Tablets Vivitrol®: Extended Release IM Injection	Generic: SL Tablets Zubsolv®: SL Tablets Bunavail®: Buccal Film Suboxone®: SL or Buccal Film	Generic: SL Tablets Probuphine®:Subdermal Implant Sublocade™: Extended Release SC Injection
Recommended Dosing for OUD	Withdrawal: Up to 40 mg per day Maintenance: 60 to 120 mg once daily	Tablet: 50 mg once daily IM injection: 380 mg once monthly	For maintenance dosing all forms are administered once daily. Maximum recommended daily dose: buprenorphine 24 mg/naloxone 6 mg	SL tablets: 8 to 16 mg once daily (recommended for pregnant women) Subdermal: 4 X 80 mg (320mg) implants inserted into one upper arm and removed after 6 months Extended release SC injection: 300 mg x 2 months followed by 100 mg once monthly

Abbreviations: DATA = Drug Addiction Treatment Act; DEA = Drug Enforcement Agency; IM = intramuscular; OTP = Opioid Treatment Program; REMS = Risk Evaluation and Mitigation Strategy; SAMHSA = Substance Abuse and Mental Health Services Administration; SC = subcutaneous, SL = sublingual

Clinically important outcomes for studies that assess efficacy of substance use disorders can include: treatment retention/completion; illicit substance use or any alcohol consumption; risk behaviors (injecting, sexual, polysubstance use, overdoses, hospital admissions); quality of life as assessed by validated scales (e.g. World Health Organization (WHO) Quality of Life scale), employment, physical health as assessed by validated scales (e.g., 36-item Short Form), adverse effects and aberrant opioid-related behaviors (e.g., multiple prescribers, lost medications, or unauthorized dose increases).²⁵ Validated clinical scales that measure opioid withdrawal symptoms, for example, the Objective Opioid Withdrawal Scale (OOWS), SOWS, and Clinical Opioid Withdrawal Scale (COWS), may be used to

assist in the evaluation of patients with opioid use disorder.²⁶ The SOWS-Gossop is a 10 item assessment in which patients use a 4 point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) to rate their withdrawal symptoms in the previous 24 hours.²⁷ Studies indicate that a change score of 2–4 points on the SOWS-Gossop scale is clinically meaningful improvement.²⁸ Symptoms assessed on the SOWS-Gossop questionnaire include: feeling sick, stomach cramps, muscle spasms, feeling cold, heart pounding, muscle tension, aches and pains, yawning, runny eyes, and insomnia.²⁷ Certain relevant symptoms of withdrawal including vomiting, sweating, agitation, diarrhea, depression, and anxiety are not assessed by the SOWS scale, which is a drawback of this instrument.²⁹ The OOWS-Handelsman is a clinician-rated assessment of physical signs of withdrawal which ranges from 0 to 13 points.²⁹

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

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

New Systematic Reviews:

Cochrane Review: Alpha2-adrenergic Agonists for Management of Opioid Withdrawal

A high quality systematic review and meta-analysis evaluated the evidence for the effectiveness of alpha2-adrenergic agonists (clonidine, lofexidine, and guanfacine) in symptomatic management of the acute phase of opioid withdrawal.² The literature search was completed through November 2015 and found 26 randomized controlled trials involving opioid-dependent participants in which an alpha2-adrenergic agonist was compared to another adrenergic agonist, placebo, or a tapering methadone regimen.² In total, 607 participants were treated with clonidine, 215 were treated with lofexidine, and 174 received guanfacine.² Treatment was scheduled to last for one to two weeks in most studies; the shortest duration was 3 days, and the longest was 30 days.² Most of the trials were conducted on inpatients, 7 studies were in an outpatient setting.² The majority of subjects were withdrawing from heroin or a short acting opioid. Outcomes of interest included the withdrawal syndrome experienced, duration of treatment, occurrence of adverse effects, and completion of treatment. The authors reported no conflicts of interest.

Moderate quality evidence compared alpha2-adrenergic agonists with placebo.² Based on three studies with 148 participants, completion of withdrawal treatment was significantly more likely with an adrenergic agonist compared with placebo (RR 1.95; 95% CI 1.34 to 2.84).² Severe withdrawal was significantly less likely with adrenergic agonist treatment compared with placebo (RR) 0.32; 95% CI 0.18 to 0.57).² Absolute risk reduction was not calculated by the authors. None of the studies reported the average time in treatment, but 2 studies reported that more participants receiving placebo dropped out within the first week of treatment.² One of the trials reported sedation and dry mouth to be approximately twice as common in participants treated with clonidine, compared with participants who received placebo.² In another trial blood pressure was significantly decreased in the lofexidine group on days four to seven of treatment.² Asthenia, dizziness, hypotension (18% versus 0%) and insomnia (42% versus 9%) all occurred more frequently in the lofexidine group compared to placebo.²

The Cochrane reviewers found insufficient data were available to evaluate the relative effectiveness of clonidine and lofexidine in terms of rates of completion of withdrawal treatment.² Furthermore, there are insufficient data available to support a conclusion on the efficacy of guanfacine in managing OUD.²

For the comparison of alpha2-adrenergic agonists with tapering doses of methadone, evidence from 9 studies including 659 participants was evaluated as low to moderate quality.² The key reasons for the low quality assessment were due to: 1) small numbers of studies reporting some outcomes; 2) low rates of occurrence of some events (for example drop-out due to adverse effects); and 3) variability between studies.² For these reasons, only moderate quality evidence will be described in this report. Three moderate quality studies including 119 participants indicated peak withdrawal scores and mean withdrawal severity were similar (SMD=0.22; 95% CI -0.02 to 0.46 and SMD=0.13; 95% CI -0.24 to 0.49, respectively).² The mean duration of treatment was significantly longer for the group treated with reducing doses of methadone compared to adrenergic agonists (SMD -1.07; 95% CI -1.31 to -0.83; moderate quality).² The incidence of adverse effects was not significantly different between methadone and adrenergic agonists (RR 2.02; 95% CI 0.62 to 6.64; 3 trials; 203 participants; moderate quality).² The risk of drop-out due to adverse effects was not statistically significant when adrenergic agonists were compared to methadone (RR 4.48; 95% CI 0.76 to 26.34; 3 trials; 105 participants; moderate quality).² Overall, the Cochrane meta-analysis of 8 moderate quality trials indicates no significant difference in rates of completion of withdrawal treatment for alpha2-adrenergic agonists compared with tapering doses of methadone (RR 0.91; 95% CI 0.75 to 1.11; 489 participants).²

Cochrane Review: Buprenorphine for Managing Opioid Withdrawal

A moderate quality systematic review and meta-analysis assessed the comparative evidence for buprenorphine in management of opioid withdrawal.¹ The summary includes 27 studies published through December 2016 involving 3048 participants. Fourteen trials compared buprenorphine to alpha2-adrenergic agonists (clonidine or lofexidine), 6 studies compared buprenorphine versus methadone, and 7 studies compared different buprenorphine dosing regimens.¹ Outcomes of interest included intensity of withdrawal, duration of treatment, treatment completion rates, and adverse effects. In most of the studies, participants were withdrawing from heroin, only one study evaluated participants withdrawing from oxycodone.¹ Nine of the 27 studies included in the review reported using sublingual buprenorphine tablets, and an additional five studies used the combination buprenorphine-naloxone tablets.¹ Three trials administered buprenorphine as a sublingual solution and three studies administered intramuscular buprenorphine injections.¹ Six trials did not report details of which buprenorphine formulation was used in their investigation.¹ None of the studies evaluated the film preparation of buprenorphine. The authors reported no conflicts of interest.

A meta-analysis of 5 moderate quality trials supports a conclusion of no difference between buprenorphine and methadone for withdrawal completion rates (RR 1.04; 95% CI 0.91 to 1.20; N=457).¹ A meta-analysis was not possible to evaluate the intensity of the outcome or duration of withdrawal treatment.¹ Three studies stated there were no significant adverse effects in either the buprenorphine or methadone groups; the other studies did not comment on adverse effects.¹

There is insufficient evidence to make conclusions on the safety and efficacy of different buprenorphine dosing regimens in managing symptoms associated with withdrawal in patients with OUD.¹ No meta-analysis was possible to assess different dosing regimens of buprenorphine for intensity of withdrawal, duration of withdrawal treatment, and nature of adverse effects.

Fourteen studies compared buprenorphine (n=750) to clonidine (n=512) or lofexidine (n=103).¹ Relative to clonidine or lofexidine, buprenorphine was associated with a lower average withdrawal score (indicating less severe withdrawal) during the treatment episode with an effect size that is considered to be small to moderate (SMD -0.43; 95% CI -0.58 to -0.28; N=902; studies=7; moderate quality).¹ Patients receiving buprenorphine stayed in treatment for longer than

adrenergic agonists (mean days in treatment with buprenorphine ranged from 25% to 97%; mean days in treatment with adrenergic agonists ranged from 21% to 70%; SMD 0.92, 95% CI 0.57 to 1.27; N=558; studies=5; moderate quality) and were more likely to complete withdrawal treatment (RR 1.59, 95% CI 1.23 to 2.06; N=1264; studies=12; moderate quality).¹ The authors did not report absolute risk reduction for these outcomes. There was no significant difference between buprenorphine and alpha2-adrenergic agonists in terms of the number of participants experiencing adverse effects.¹

Canadian Agency for Drugs and Technologies in Health: Buprenorphine Formulations: A Review of Comparative Clinical Effectiveness

In 2017 CADTH published a rapid response report to evaluate the comparative effectiveness of monotherapy buprenorphine and buprenorphine-naloxone formulations (e.g., sublingual films, sublingual tablets, implants,) for treatment of OUD.³ The review focused on evaluating the comparative evidence for different buprenorphine formulations published from 2012 through June 2017, which is quite sparse.³ Five RCTs and 3 observational, retrospective cohort analyses were identified for the CADTH publication. Of the 5 RCTs which met inclusion criteria, all but two were industry-sponsored and there were limitations with respect to study design (e.g., non-inferiority, open-label), clinically relevant outcomes and treatment duration.³ No systematic reviews comparing the various buprenorphine formulations were identified.³ There were no Canadian or American clinical practice guidelines identified to specifically compare and evaluate different formulations of buprenorphine for OUD.³

In two of the RCTs, patients were randomized to receive either the rapidly dissolving buprenorphine-naloxone sublingual tablet for the entire trial or buprenorphine sublingual tablets for 2 days followed by buprenorphine-naloxone film for the remainder of the trial.³ The treatment duration in these RCTs ranged from 22 days to 29 days.³ One additional RCT conducted over 31 days compared buprenorphine-naloxone film to the buprenorphine-naloxone sublingual tablet.³ In 2 RCTs the intervention was four buprenorphine implants compared to placebo and evaluated over 24 to 26 weeks.³ However, open-label sublingual buprenorphine-naloxone or buprenorphine was available as a rescue medication to all included patients.³⁰ The addition of open-label rescue medication (buprenorphine or buprenorphine-naloxone) may have confounded the assessment of the efficacy of the implants.³

All the buprenorphine formulations examined in the selected studies showed a similar clinical response in patients with opioid use disorder, with significantly higher rates of abuse, misuse and diversion found in sublingual buprenorphine-naloxone tablet formulations.³ The use of buprenorphine implants was associated with high rates of treatment retention.³ The rates of adverse effects were low among buprenorphine formulations with no significant differences observed.³ The findings indicate that the use of newer available buprenorphine formulations may be safe to use in this population, but the included trials were relatively short in duration and may have been underpowered to detect rarer adverse effects.³ Larger studies with longer treatment durations are required to better understand the efficacy and safety profiles of these newer formulations.³ Conclusions on the best practices regarding the use of buprenorphine formulations for patients with opioid use disorder cannot be drawn as no relevant systematic reviews or evidence-based guidelines which consider all available evidence were identified by the CADTH authors.³

New Guidelines:

Canadian Research Initiative in Substance Misuse: Management of Opioid Use Disorders: A National Clinical Practice Guideline.

The Canadian Research Initiative in Substance Misuse (CRISM) was funded by the Canadian Institute of Health Research (CIHR) to develop a national clinical practice guideline on management of OUD.⁵ Four interdisciplinary regional networks identified relevant experts and stakeholders to participate on the 43-member review committee. The guideline research and development was entirely funded through the CIHR-funded CRISM network without pharmaceutical industry support.⁵ No current or ongoing direct competing interests were disclosed by the 43 members of the review committee or the four CRISM principal investigators on screening for participation in the review committee.⁵ A structured literature review approach was used to develop recommendations using the

Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.⁵ Using the AGREE-II instrument, the guidelines were appraised as having high methodological quality.⁸ Key recommendations for first and second-line OUD treatments in adults based on high quality evidence include:

- While shown to be essentially as efficacious as methadone in clinical trials, buprenorphine–naloxone has several safety advantages over methadone including a reduced risk of fatal overdose because of its lower potential for respiratory depression.⁵ Given the superior safety profile of buprenorphine–naloxone and its potential for flexible take-home dosing in comparison to other opioid agonist medications, initiate opioid agonist treatment (with buprenorphine–naloxone whenever feasible), to reduce the risk of toxicity, morbidity and death, and to facilitate safer take-home dosing (strong recommendation).⁵
- For individuals responding poorly to buprenorphine–naloxone, consider transition to methadone treatment (strong recommendation).⁵
- Initiate opioid agonist treatment with methadone when treatment with buprenorphine–naloxone is not the preferred option such as those individuals with a high opioid tolerance, severe opioid withdrawal symptoms or those requiring supervised administration due to poor adherence (strong recommendation).⁵

The recommendation for use of oral naltrexone as an adjunct medication in treating OUD is a weak recommendation based on low quality evidence.⁵ Recommendations for the role of extended release naltrexone injection in treating OUD are not included in these guidelines because this medication is not widely available in Canada.⁵ Best practices for treating specific populations, including adolescents and young adults, the elderly, individuals living with concurrent chronic pain, incarcerated individuals, and indigenous populations are not addressed in these guidelines. Additionally, the publication offers a brief overview of the available evidence specifically related to OUD treatment in pregnant women; however, it emphasizes the importance of specialist referral and further research and training in this area.⁵

New Formulations or Indications:

1. The FDA approved buprenorphine extended-release injection (Sublocade™) in November 2017 to treat patients with moderate-to-severe OUD who have first received treatment with transmucosal buprenorphine for at least 7 days.⁶ The application for this formulation was given priority review and approved through the FDA's fast track process, which is designed to expedite the review of drugs that fill an unmet medical need. Buprenorphine extended-release injection is a 100 or 300 mg subcutaneous injection administered once a month by a HCP.⁶ The safety and efficacy of extended-release buprenorphine were evaluated in two clinical studies (one randomized, placebo-controlled clinical trial and one open-label clinical trial) of 848 adults with a diagnosis of moderate-to-severe OUD who began treatment with buprenorphine/naloxone sublingual film.⁶ Response to therapy was measured by urine drug screening and self-reporting of illicit opioid use during the six-month treatment period. Results indicated that buprenorphine-treated patients had more weeks without positive urine tests or self-reports of opioid use, and a higher proportion of patients had no evidence of illicit opioid use throughout the treatment period, compared to the placebo group.⁶ The most common side effects from treatment with extended-release buprenorphine injection include constipation, nausea, vomiting, headache, drowsiness, injection site pain, pruritus at the injection site and abnormal liver function tests.⁶ The safety and efficacy of extended-release buprenorphine have not been established in children or adolescents less than 17 years of age or adults over the age of 65 years.⁶

Sublocade™ has a boxed warning regarding the risks of intravenous self-administration.⁶ If the product were to be administered intravenously rather than subcutaneously, the solid mass the drug is contained within could cause occlusion, tissue damage or embolus.⁶ Sublocade™ must be prescribed and dispensed as part of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the product is not distributed directly to patients.⁶ Sublocade will be provided to HCPs through a restricted program, administered only by HCPs in a health care setting, and will require health care settings and pharmacies that dispense Sublocade™ to complete an enrollment form attesting that they have procedures in place to ensure that Sublocade™ is dispensed only to HCPs and not directly to patients.⁶ The FDA is requiring postmarketing studies to assess which patients would benefit from a higher Sublocade™ dosing regimen, to determine whether extended-

release buprenorphine can be safely initiated without a dose stabilization period of sublingual buprenorphine, to assess the feasibility of administering the extended-release injection at a longer inter-dose interval than once-monthly, and to determine a process for transitioning patients with long-term stability on a transmucosal buprenorphine to a monthly dose of extended-release buprenorphine without the use of a higher dose (300mg) for the first two months of treatment.

2. In April 2017, Bunavail® (buprenorphine and naloxone) buccal film received expanded approval to use this product during the induction phase of treatment for patients dependent on heroin or short-acting opioid products.⁷ For patients dependent on methadone or long-acting opioid products, combination therapy with buprenorphine and naloxone has not been adequately studied.⁷ For this reason, buprenorphine monotherapy is recommended in patients taking long-acting opioids starting treatment for OUD.⁷ The previous indication for Bunavail® only addressed administration during the maintenance phase of OUD treatment.⁷

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts³¹

Generic Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Buprenorphine (all products)	2/2018	Warnings and Precautions	Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose and death. As a routine part of orientation to buprenorphine treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, opioid analgesics, and alcohol.
Methadone (all products)	2/2018	Warnings and Precautions	Concomitant use of methadone and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose and death. Reserve concomitant prescribing of benzodiazepines or other CNS depressants in patients in methadone treatment to those for whom alternatives to benzodiazepines or other CNS depressants are inadequate. Follow patients for signs and symptoms of respiratory depression and sedation. If the patient is visibly sedated, evaluate the cause of sedation and consider delaying or omitting daily methadone dosing.

Randomized Controlled Trials:

A total of 141 citations were manually reviewed from the initial literature search. After further review, 140 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 1 trial is summarized in **Table 3** below. The full abstract is included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Law et al ⁴	1. Buprenorphine/naloxone 4mg/1mg Vs.	80 opiate-dependent subjects	Compare efficacy of 1 vs 2 on opiate withdrawal symptoms as assessed via the OWS during detoxification phase	Mean OWS 1. 16.7 2. 14.0 Mean Difference: 2.7

	2.Methadone 30 mg/lofexidine PRN			95% CI 3.0 to 8.3 p=0.01
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Abbreviations: CI = Confidence Interval; OWS = Opiate Withdrawal Scale; PRN = as needed

NEW DRUG EVALUATION: Lofexidine (Lucemyra™)

Lofexidine, a centrally acting alpha2-adrenergic receptor agonist, is structurally and pharmacologically similar to clonidine.¹⁰ A new drug application submitted to the FDA in 1983 for use of lofexidine in hypertension did not receive approval due to lack of efficacy.²⁹ However, in 1992 Britannia began marketing lofexidine in the United Kingdom under the trade name Britlofex™ for the treatment of symptoms in patients undergoing opioid detoxification.²⁹ In May 2018, lofexidine (Lucemyra™) received FDA approval for short-term (up to 14 days) mitigation of severe opioid withdrawal symptoms in adults to facilitate abrupt opioid discontinuation.¹⁰ Lofexidine reduces the release of norepinephrine and decreases sympathetic tone, which lessens the symptoms of withdrawal.¹⁰ Lofexidine may not completely prevent withdrawal symptoms and is not a treatment for OUD as a single agent, but can be used as part of a broader, long-term treatment plan for managing OUD.¹⁰ See **Appendix 4** for Highlights of Prescribing Information from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The FDA approval of lofexidine was based primarily on efficacy and safety evidence from 2 inpatient phase 3 clinical trials. Study 3003 and Study 3002 were completed in a total of 866 patients with opioid addiction. Only the results of Trial 3002 have been published; information about Trial 3003 was accessed at clinicaltrials.gov (<http://clinicaltrials.gov/ct2/show/NCT01863186>) and the FDA website.²⁹

Study 3002 was an inpatient, randomized, multicenter, double-blind, placebo-controlled study conducted at 15 U.S. sites in 264 patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, or oxycodone).⁹ Subjects were randomized 1:1 to receive lofexidine 2.88 mg/day (n=134) or placebo tablets (n=130) for 5 days, followed by an additional 2 days of treatment with placebo prior to discharge on Day 8.⁹ Most participants were white males (average age 37 years); 60% reported intravenous opioid use, the most common being heroin.⁹ Patients also had access to a variety of support medications for withdrawal symptoms including guaifenesin, an antacid combination, dioctyl sodium sulfosuccinate, psyllium hydrocolloid, bismuth sulfate, zolpidem, acetaminophen, and nicotine replacement therapy. Placebo-treated subjects used more of each concomitant support medication than lofexidine-treated subjects.⁹ Overall, 37% of participants allocated to lofexidine and 27% allocated to placebo completed the 8-day treatment course; the overall retention rate was 32.2%.⁹ The primary reason for study withdrawal was subject request (35% vs. 40%; lofexidine vs. placebo) and lack of efficacy (13% vs. 28%; lofexidine vs. placebo).⁹ The higher incidence of discontinuations in the placebo group due to lack of efficacy is consistent with lofexidine having a treatment effect on withdrawal symptoms.²⁹

The co-primary efficacy endpoints in Study 3002 were mean SOWS-Gossop total score on day 3 of treatment and time to study dropout. Day 3 was chosen to be at or near the anticipated peak of withdrawal as per FDA recommendation.⁹ The SOWS-Gossop assessment is a 10 item, patient-reported outcome instrument. Each item represents a symptom and is evaluated on a scale ranging from a total score of 0 (no symptoms) to 30 (severe symptoms).²⁷ A higher score indicates a greater withdrawal symptom severity. Studies indicate that a change score of 2–4 points on the SOWS-Gossop scale is clinically meaningful improvement.²⁸ For this trial, the investigators assumed a minimal clinically significant difference of 5 points.⁹ The mean SOWS-Gossop scores on day 3 were 8.67 and 6.32 for placebo and lofexidine, respectively, which demonstrated a statistically significant difference between the 2 arms (LSMD = -2.24, 95% CI -3.88 to -0.6; p=0.009).²⁹ However, this assessment did not meet the pre-specified clinical significance of a 5 point difference. Time-to-dropout was chosen as a global assessment of

efficacy (i.e. treatment retention) by the investigators.⁹ Each study day was divided into four 6 hour time quadrants (i.e., 6am–12pm; 12pm–6pm; 6pm–12am; and, 12am–6am) and time-to-dropout was measured as the number of 6 hour time quadrants until withdrawal or completion of the 5-day treatment phase.⁹ Early termination was statistically higher in the placebo group compared to lofexidine as assessed by the mean number of time quadrants (6.4 vs. 6.9 respectively; $p=0.0034$).⁹ However, the calculated difference was 0.5 time quadrants, or 3 hours, which is not a clinically significant difference in time to withdrawal.

Secondary endpoints included mean SOWS-GOSSOP scores for Days 1 through 5 and the proportion of patients that completed 5 days of treatment. The estimated treatment effect on average SOWS-Gossop scores from Day 1 through Day 5 also showed a significant difference between lofexidine and placebo. The overall mean SOWS-Gossop score from Day 1 through Day 5 for placebo was 10.64 compared to 8.31 for lofexidine (LSMD -2.33; 95% CI -3.42 to -1.25; $p<0.001$).²⁹ Although this difference was statistically significant, it did not meet the minimal clinical difference of a change in 5 points on the SOWS-Gossop scale. The proportion of 5-day treatment completers was significantly higher in the patients receiving lofexidine (49%) compared with patients receiving placebo (33%), $p=0.009$; number needed to treat (NNT) = 7.⁹ Early termination of treatment was significantly more common in the placebo group compared to lofexidine (61% vs. 44% of subjects, respectively).⁹ Missing data was estimated using a multiple imputation technique.

Unpublished Trial

Study 3003 was a dose-response study conducted in 602 patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, or oxycodone) at 18 U.S. sites.²⁹ Part 1 of the study was an inpatient, double-blind study in which subjects were randomized 3:3:2 to lofexidine 2.16 mg/day ($n=229$), lofexidine 2.88 mg/day ($n=222$) or placebo ($n=151$) for 7 days.²⁹ Most of the participants were white males (average age 35 years), primarily dependent on heroin. Patients also had access to a variety of support medications for withdrawal symptoms similar to Study 3002. Overall, placebo-treated subjects used more concomitant medications than lofexidine-treated subjects.²⁹ A total of 225 participants (37.3%) completed the double-blind phase of the study. The reason most patients in the placebo arm withdrew from the study was due to lack of efficacy. Patients who withdrew from the lofexidine arms reported lack of efficacy or an adverse effect related to the study medication. Part 2 of this study enrolled patients who completed the first 7 days of treatment into an open-label, variable lofexidine dose trial for an additional 7 days in either an inpatient or outpatient setting as determined by the investigator and the patient.²⁹ A total of 83 participants (13.8%) enrolled in the second open-label phase of the study and 70 (84.3%) of those subjects completed the open-label phase.²⁹

The primary efficacy endpoints in Trial 3003 were the mean SOWS-Gossop total score on day 1 through 7 of treatment and the proportion of patients that completed 7 days of treatment.²⁹ The mean SOWS-Gossop scores for days 1 through 7 were 5.23, 4.07, and 3.8 for placebo, lofexidine 2.16 mg and lofexidine 2.88 mg, respectively.²⁹ The LSMD from placebo and lofexidine 2.16 mg was -0.21 (95% CI -0.37 to -0.04; $p = 0.009$) and the LSMD from placebo and lofexidine 2.88 mg was -0.26 (95% CI -0.44 to -0.09; $p = 0.003$).²⁹ The change in SOWS-Gossop scores between placebo and lofexidine was statistically significant for both dosing regimens of lofexidine. There was no significant difference observed between the two doses of lofexidine.²⁹ The proportion of 7-day treatment completers was significantly higher for both lofexidine arms compared to placebo. Twenty-eight percent of patients receiving placebo completed 7 day treatment compared to 42% of patients receiving lofexidine 2.16 mg (Odds Ratio (OR) 1.85; 95% CI 1.18 to 2.88; $p=0.007$) and 40% of patients receiving lofexidine 2.88 mg (OR 1.71; 95% CI 1.09 to 2.67; $p=0.019$).²⁹ There was no significant difference between the two doses of lofexidine in 7 day completion rates.²⁹

Trial Limitations:

The published trial has a number of limitations which reduced the assessment of study quality to poor. The co-primary endpoints in the published trial showed a statistical difference in reducing withdrawal symptoms and time-to-dropout as measured in 6 hour time intervals. However, the clinical significance of the

change in SOWS-Gossop score did not meet the minimal clinically significant difference of 5 points. The time to study dropout revealed a difference of 3 hours which is not a clinically significant difference in time to withdrawal. Furthermore, there was substantial attrition (63-73%) from this trial due to patients requesting to withdraw from study either due to withdrawal symptoms or for reasons unrelated to withdrawal symptoms. Missing data were estimated using a multiple imputation technique. Conflict of interest for study authors was disclosed and 50% of the authors are either an employee or a consultant for US WorldMeds.

Since the data from Trial 3003 is unpublished, the methodological quality of the trial cannot be fully assessed. Both trials limited enrollment to subjects acutely withdrawing from heroin and short-acting prescription opioids. The efficacy of lofexidine in patients undergoing a taper of opioids or patients discontinuing long-acting opioids has not been evaluated. Furthermore, there are not adequate data to assess the risks of lofexidine beyond 7 days of consecutive use. For this reason, the FDA recommends a postmarketing study of lofexidine in patients discontinuing opioids using a slow taper dosing regimen beyond 7 days. Finally, no comparative data of lofexidine to other treatment options such as clonidine are available.

Clinical Safety:

In clinical trials the most commonly reported adverse reactions with lofexidine were orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.¹⁰ Upon cessation of treatment with lofexidine, subjects were observed to experience rebound blood pressure elevations. These observed risks are consistent with the known effects of alpha-2 adrenergic agonists.²⁹ **Table 4** presents the incidence of adverse events that occurred in 10% or greater of patients treated with lofexidine and for which the incidence in patients treated with lofexidine was greater than in patients treated with placebo. Rates of serious and severe adverse effects requiring treatment discontinuation were relatively low. The incidence of treatment emergent adverse effects is outlined in **Table 5**.

Table 4 : Adverse Reactions Reported by ≥ 10% of Lofexidine-Treated Patients and More Frequently than Placebo¹⁰

Adverse Reaction	Lofexidine 2.16 mg/day, % (n=229)	Lofexidine 2.88 mg/day, % (n=222)	Placebo, % (n=151)
Insomnia	51	55	48
Orthostatic Hypotension	29	42	5
Bradycardia	24	32	5
Hypotension	30	30	1
Dizziness	19	23	3
Somnolence	11	13	5
Sedation	13	12	5
Dry Mouth	10	11	0

Table 5: Treatment Emergent Adverse Effects observed in clinical trials of lofexidine compared to placebo¹⁰

Treatment Emergent Adverse Effect (TEAE)	Lofexidine 2.16 mg/day, % (n=229)	Lofexidine 2.88 mg/day, % (n=222)	Placebo, % (n=151)
TEAE related to opioid withdrawal	79	80	85
TEAE not related to opioid withdrawal	77	79	40
TEAE leading to study discontinuation	19	25	29
Serious TEAE	0	2	1

Severe TEAE	4	8	7
Deaths	0	0.5	0

The approved label for lofexidine contains a warning about the risk of QT prolongation associated with lofexidine administration.¹⁰ The observed increase in QT interval in the studies conducted by the manufacturer does not suggest that the effect is clinically significant and did not appear to be dose-related.²⁹ However, there is a publication in the literature that reports that three subjects had clinically significant QT prolongation while receiving concurrent lofexidine and methadone.²⁹ In addition, there is one postmarketing case of torsade de pointes in a patient that was receiving lofexidine.²⁹ Overall, the concern for QT prolongation with lofexidine appears to be mainly limited to settings in which it would be co-administered with other medications that lead to QT prolongation (e.g., methadone).²⁹

Look-alike / Sound-alike Error Risk Potential: Nothing reported

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Reduction of opioid withdrawal symptoms
- 2) Completion of detoxification program
- 3) Serious adverse events
- 4) Study withdrawal due to an adverse event
- 5) Long term abstinence
- 6) Quality of life

Primary Study Endpoint:

- 1) Reduction of opioid withdrawal symptoms as assessed by SOWS-Gossop score on Day 3 of therapy

Table 5. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Alpha-2 adrenergic agonist
Oral Bioavailability	72% oral absorption: peak plasma levels observed 3-5 hour after administration
Distribution and Protein Binding	Mean volume of distribution = 480 liters; plasma protein binding = 55%
Elimination	Approximately 93.5% of the dose was recovered in urine post-dose. Renal elimination of unchanged drug accounts for approximately 15% to 20% of the administered dose.
Half-Life	12 hours
Metabolism	Primarily metabolized by CYP2D6 and to a lesser extent by CYP1A2 and CYP2C19

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.Study 3002 Gorodetzky, et al ⁹ DB, PC, MC, PG N = 264 Three phases of treatment over 8 days: 1.Screening phase as an outpatient days -7 to -1 2. Inpatient treatment phase on days 1-5 3.Post-treatment inpatient phase on days 6-7 15 sites in the United States from 2006-2007	1. Lofexidine 2.88 mg/day (0.72 mg PO QID) on days 1-5, followed by placebo (4 tablets) on days 6-7 2. Placebo (4 tablets) PO QID on days 1-5, followed by placebo (4 tablets) PO QID on day 6-7 (Lofexidine supplied as 0.18mg tablets)	<u>Demographics:</u> -Mean age: 37 yo -Gender: 76% male -Ethnicity: White - 53% Black – 24% Hispanic – 23% -Primary Opioid Use: Heroin – 62% Oxycodone – 21% Hydrocodone – 15% <u>Key Inclusion Criteria:</u> -Age ≥18 yo -Opioid dependent according to DSM-IV criteria -Use of heroin, morphine or any opioid with a similar half-life for ≥21 of the past 30 days -OOWS score ≥2 at baseline -Positive urine toxicology screen for opiates and negative for methadone and buprenorphine <u>Key Exclusion Criteria:</u> -Serious medical or psychiatric illness (seizures, insulin-dependent diabetes, hepatic or renal disease) -Self reported AIDS, active tuberculosis, or active syphilis -Dependence on any psychoactive substance -Abnormal cardiovascular exam (prolonged QT, hypertension, hypotension, bradycardia, history of MI) -Use of methadone or buprenorphine within 14 days -Use of psychotropics, analgesics, anticonvulsants, anti-hypertensives, anti-	<u>ITT:</u> 1.134 2.130 <u>PP:</u> 1.50 (37%) 2.35 (27%) <u>Attrition:</u> 1.84 (63%) 2.95 (73%)	<u>Primary Endpoint:</u> Mean SOWS-Gossop total score, day 3 1.6.32 2.8.67 LSMD = -2.24 95% CI -3.88 to -0.60 p=0.009 Mean time to Dropout (Number of 6 hour time quadrants) 1. 6.9 2. 6.4 p = 0.0034 95% CI NR <u>Secondary Endpoints:</u> SOWS-Gossop score from Day 1 through Day 5 1.8.31 2.10.64 LSMD -2.33 95% CI -3.42 to -1.25 p < 0.001 Number of treatment completers on Day 5 1.66 (49%) 2. 43 (33%) p=0.009 95% CI NR	NA NA NA NNT = 7	<u>Outcome:</u> <u>Any TEAE</u> 1.97% 2.94% p=0.25 <u>Severe TEAE</u> 1.23% 2.29% p value NR <u>Study Withdrawal due to TEAE</u> 1.4% 2.5% p value NR <u>Insomnia</u> 1.44% 2.42% p=0.80 <u>Hypotension</u> 1.25% 2.1% p<0.01 <u>Dizziness</u> 1. 22% 2.7% p<0.01 <u>Bradycardia</u> 1.10% 2.2% p<0.01 95% CI NR for all outcomes	NS NA NA NS 24/5 15/7 8/13	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> Low. Patients randomized by centralized ITTRS. Patients were allocated in a 1:1 ratio. Demographics similar between groups at baseline. <u>Performance Bias:</u> Unclear. Placebo and lofexidine matched to maintain blinding. Study protocol not available in supplemental materials for assessment. Not clear if protocol was followed at all 15 sites. <u>Detection Bias:</u> Low. Quadruple blinded: participant, care provider, investigator, and outcomes assessor. <u>Attrition Bias:</u> High. High attrition rate (63-73%) due to patient request to withdraw from study. Missing data estimated using a multiple imputation technique <u>Reporting Bias:</u> Unclear. Study protocol not available in supplemental materials for assessment of outcome reporting. <u>Other Bias:</u> Study conducted by US WorldMeds, NIDA, and Department of Veterans Affairs. US WorldMeds funded the study, participated in study design, monitoring of study sites, administration of trial, writing the report and submission for publication. Conflict of interest for study authors disclosed. 50% of the authors are either an employee or a consultant for US WorldMeds. Applicability: <u>Patient:</u> High proportion of young adult, White males dependent on short acting opioids in acute withdrawal in an inpatient setting. Cannot extrapolate results to patients on long acting opioids or tapered withdrawal in an outpatient setting. <u>Intervention:</u> Used the higher dose of lofexidine as this trial was completed prior to dose-ranging trial. <u>Comparator:</u> Placebo used as comparator. May have been more helpful to compare lofexidine to clonidine. <u>Outcomes:</u> SOWS-Gossop score validated in other clinical trials. Minimal clinical difference defined as 5 points by the investigators. Time to dropout a co-primary endpoint. Double blind component of trial

		arrhythmics, antiretroviral, or cholesterol lowering agents within 4 weeks prior to study enrollment						only conducted over 5 days, limiting assessment of risks of therapy over 14 days. <u>Setting:</u> 15 U.S. sites
<p>Abbreviations : AIDS = Acquired Immune Deficiency Syndrome; ARR = absolute risk reduction; CI = confidence interval; COI = conflict of interest; DB = double blind; DSM-IV = Diagnostic and Statistical Manual for Mental Disorders Fourth Edition; ITT = intention to treat; ITTRS = interactive touch tone randomization system; LSMD = Least Squares Mean Difference; MC = multi-center; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NIDA = National Institute on Drug Abuse; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OOWS = Objective Opiate Withdrawal Scale; PBO = placebo; PC = placebo controlled; PG = parallel group; PO = oral; PP = per protocol; QID = four times a day; SOWS = short opiate withdrawal scale; TEAE = treatment emergent adverse event; YO = years old</p>								

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Appendix 1: Current Preferred Drug List

Route	Form	Brand	Generic	PDL
ORAL	TABLET DR	ACAMPROSATE CALCIUM	ACAMPROSATE CALCIUM	Y
INTRAMUSC	SUS ER REC	VIVITROL	NALTREXONE MICROSPHERES	Y
SUBLINGUAL	TAB SUBL	BUPRENORPHINE-NALOXONE	BUPRENORPHINE HCL/NALOXONE HCL	Y
SUBLINGUAL	FILM	SUBOXONE	BUPRENORPHINE HCL/NALOXONE HCL	Y
SUBLINGUAL	TAB SUBL	ZUBSOLV	BUPRENORPHINE HCL/NALOXONE HCL	Y
ORAL	TABLET	NALTREXONE HCL	NALTREXONE HCL	Y
ORAL	TABLET	ANTABUSE	DISULFIRAM	N
ORAL	TABLET	DISULFIRAM	DISULFIRAM	N
SUBLINGUAL	TAB SUBL	BUPRENORPHINE HCL	BUPRENORPHINE HCL	N
BUCCAL	FILM	BUNAVAIL	BUPRENORPHINE HCL/NALOXONE HCL	N
SQ	SOLER SYR	SUBLOCADE	BUPRENORPHINE	N
IMPLANT	IMPLANT	PROBUPHINE	BUPRENORPHINE HCL	
ORAL	TABLET	LUCEMRYA	LOFEXIDINE	

Appendix 2: Abstracts of Comparative Clinical Trials

Law FD, Diaper AM, Melichar JK, Coulton S, Nutt DJ, Myles JS. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: A randomised controlled trial of low dose short-term opiate-dependent individuals. *Journal of Psychopharmacology*. 2017; 31(8):1046-1055.

Buprenorphine/naloxone, methadone and lofexidine are medications with utility in the treatment of opiate withdrawal. We report the first randomised controlled trial to compare the effects of these two medications on withdrawal symptoms and outcome during opiate induction/stabilisation and detoxification. A double-blind randomised controlled trial was conducted in an outpatient satellite clinic of a specialist drug service. Eighty opiate dependent individuals meeting DSM-IV criteria for opiate dependence, using $\leq \frac{1}{2}$ g heroin smoked/chased or $\frac{1}{4}$ g heroin injected or ≤ 30 mg methadone, with ≤ 3 years of opioid dependency, underwent a short-term opiate treatment programme involving induction/stabilisation on methadone 30mg or buprenorphine/naloxone 4mg/1mg, followed by detoxification (where the methadone group was assisted by lofexidine). The main outcome measures were urine drug screens for opiates and withdrawal and craving questionnaires. There were no overall differences in positive urine drug screens and drop-outs during any phase of the study. During induction/stabilisation, withdrawal symptoms subsided more slowly for buprenorphine/naloxone than for methadone, and craving was significantly higher in the buprenorphine/naloxone group ($p < 0.05$, 95% confidence interval -3.5 , -0.38). During detoxification, withdrawal symptoms were significantly greater and the peak of withdrawal was earlier for the methadone/lofexidine group than the buprenorphine/naloxone group ($p < 0.01$, 95% confidence interval 3.0, 8.3). Methadone/lofexidine and buprenorphine/naloxone had comparable outcomes during rapid outpatient stabilisation and detoxification in low dose opiate users.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 5 2018

1 exp Buprenorphine/	4617
2 exp Buprenorphine, Naloxone Drug Combination	211
3 exp Naltrexone/	7426
4 exp Prescription Drug Misuse	1314
5 exp Opioid-Related Disorders	23081
6 Substance-Related Disorders	88730
7 1 ore 2 or 3	11870
8 4 or 5 or 6	110018
9 7 and 8	3205
10 limit 5 to (English language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	123
11 Lofexidine.mp	164

Ovid MEDLINE(R) without Revisions 1996 to July Week 5 2018

1acamprostate.mp.	740
2 exp Disulfiram/	3345
3 exp Naltrexone/	7426
4 exp Alcoholism/	72196
5 exp Substance-Related Disorders/	259680
6 exp Alcohol Deterrents/	4240
7 1 or 2	3983
8 4 or 5 or 6	261830
9 7 and 8	3901
10 limit 9 to (English language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	18

Appendix 4: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LUCEMYRA™ (lofexidine) tablets, for oral use
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

LUCEMYRA is a central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. (1)

DOSAGE AND ADMINISTRATION

- The usual LUCEMYRA dosage is three 0.18 mg tablets taken orally 4 times daily at 5- to 6-hour intervals LUCEMYRA treatment may be continued for up to 14 days with dosing guided by symptoms. (2.1)
- Discontinue LUCEMYRA with a gradual dose reduction over 2 to 4 days. (2.1)
- **Hepatic or Renal Impairment:** Dosage adjustments are recommended based on degree of impairment. (2.2, 2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 0.18 mg. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- **Risk of Hypotension, Bradycardia, and Syncope:** May cause a decrease in blood pressure, a decrease in pulse, and syncope. Monitor vital signs before dosing and advise patients on how to minimize the risk of these cardiovascular effects and manage symptoms, should they occur. Monitor symptoms related to bradycardia and orthostasis. When using in outpatients, ensure that patients are capable of self-monitoring signs and symptoms. Avoid use in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure, as well as in patients with marked bradycardia. (5.1)
- **Risk of QT Prolongation:** LUCEMYRA prolongs the QT interval. Avoid use in patients with congenital long QT syndrome. Monitor ECG in patients

with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, hepatic or renal impairment, or in patients taking other medicinal products that lead to QT prolongation. (5.2)

- **Increased Risk of CNS Depression with Concomitant use of CNS Depressant Drugs:** LUCEMYRA potentiates the CNS depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs. (5.3)
- **Increased Risk of Opioid Overdose after Opioid Discontinuation:** Patients who complete opioid discontinuation are at an increased risk of fatal overdose should they resume opioid use. Use in conjunction with comprehensive management program for treatment of opioid use disorder and inform patients and caregivers of increased risk of overdose. (5.4)
- **Risk of Discontinuation Symptoms:** Instruct patients not to discontinue therapy without consulting their healthcare provider. When discontinuing therapy, reduce dose gradually. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence \geq 10% and notably more frequent than placebo) are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact US WorldMeds at 1-833-LUCEMYRA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- **Methadone:** Methadone and LUCEMYRA both prolong the QT interval. ECG monitoring is recommended when used concomitantly. (7.1)
- **Oral Naltrexone:** Concomitant use may reduce efficacy of oral naltrexone. (7.2)
- **CYP2D6 Inhibitors:** Concomitant use of paroxetine resulted in increased plasma levels of LUCEMYRA. Monitor for symptoms of orthostasis and bradycardia with concomitant use of a CYP2D6 inhibitor. (7.4)

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

Revised: XX/2018

Lofexidine

Goal(s):

- Encourage use of substance use disorder medications on the Preferred Drug List.
- Restrict use of lofexidine under this PA to ensure medically appropriate use of lofexidine based on FDA-approved indications.

Length of Authorization:

- Up to 14 days

Requires PA:

- Lofexidine 0.18mg tablets

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication? (Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults)	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> • Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee. 	Yes: Inform prescriber of covered alternatives in class.	No: Approve for up to 14 days of total therapy. Note: FDA approved indication is for up to 14 days of therapy

P&T/DUR Review: 11/18 (DM)
Implementation: TBD

Buprenorphine and Buprenorphine/Naloxone

Goals:

- Encourage use of buprenorphine products on the Preferred Drug List.
- Restrict use of buprenorphine products under this PA to management of opioid use disorder.
- Restrict use of oral transmucosal buprenorphine monotherapy products (without naloxone) to pregnant patients or females actively trying to conceive.

Length of Authorization:

- Up to 6 months

Requires PA:

- Buprenorphine sublingual tablets
- Suboxone® and generics (buprenorphine/naloxone) film and sublingual tablets that exceed an average daily dose of 24 mg per day of buprenorphine
- Bunavail® (buprenorphine/naloxone buccal film)
- Zubsolv® (buprenorphine/naloxone sublingual tablets)
- Probuphine® (buprenorphine subdermal implants)
- Sublocade™ (buprenorphine extended-release subcutaneous injection)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
<p>1. What is the diagnosis is being treated and is the requested treatment funded by the OHP for that condition?</p> <p>Note: Treatments which appear on an unfunded line of the prioritized list are not funded by the OHP</p>	<p>Yes: Go to #2</p>	<p>No: Pass to RPh. Deny; not funded by OHP</p>

Approval Criteria		
2. Is the request for renewal of therapy previously approved by the FFS system?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is the prescription for opioid use disorder (opioid dependence or addiction)?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system (<u>e.g. individual and group counseling, intensive outpatient treatment, recovery support services, or 12-step fellowship</u>)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness. Buprenorphine therapy must be part of a comprehensive treatment program that includes psychosocial support.
5. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com), and has the prescriber verified <u>evaluated the PDMP</u> at least once in the past 6 months, <u>and verified</u> that the patient <u>is not currently</u> has not been prescribed any opioid analgesics from other prescribers?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness
6. Is the requested medication a preferred agent?	Yes: Go to #8	No: Go to #7
7. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	Yes: Inform prescriber of covered alternatives in class.	No: Go to #8
8. Is the request for the buprenorphine implant system (Probuphine)?	Yes: Go to #9	No: Go to #10

Approval Criteria

<p>9. Has the patient been <i>clinically stable</i> on 8 mg daily or less of Suboxone or Subutex (or equivalent, see Table 1) for at least 6 months?</p> <p>Note: see Table 1 for definition of clinical stability and for equivalent dosing of other buprenorphine products.</p>	<p>Yes: If <u>all</u> criteria in Table 1 met, approve 4 implants for 6 months</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>10. Is the request for extended-release subcutaneous buprenorphine injection (Sublocade™)?</p>	<p>Yes: Go to #11</p>	<p>No: Go to # 13</p>
<p>11. Is the provider registered through the Sublocade™ REMS program?</p> <p>Note: Sublocade carries a boxed warning that stipulates healthcare settings and pharmacies that order and dispense Sublocade™ must be certified in the Sublocade™ REMS program and comply with the REMS requirements due to serious harm or death if this product is administered intravenously. Prescriber offices that only order Sublocade from a certified pharmacy for a specific patient are exempt from certification. Further information is available at www.SublocadeREMS.com or call 1-866-258-3905.</p>	<p>Yes: Go to #12</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>

Approval Criteria

<p>12. Has the patient been clinically stable on a transmucosal buprenorphine-containing product at a dose of 8 to 24 buprenorphine per day (or equivalent-see note below) for a minimum of 7 days?</p> <p>Note: One Suboxone® (buprenorphine and naloxone) 8 mg/2 mg sublingual tablet provides equivalent buprenorphine exposure to one Subutex® (buprenorphine HCl) 8 mg sublingual tablet or one Bunavail® (buprenorphine and naloxone) 4.2mg/0.7 mg buccal film or one Zubsolv® (buprenorphine and naloxone) 5.7 mg/1.4 mg sublingual tablet</p>	<p>Yes: Approve 300mg once a month for 2 months followed by 100mg once a month for 6 months total</p> <p>Increasing the maintenance dose to 300mg once a month may be considered for patients who tolerate the 100mg dose but do not demonstrate a satisfactory clinical response as evidenced by self-reported illicit opioid use or urine drug screens positive for illicit opioid use.</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>
<p>13. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., >24 mg/day or >48 mg every other day)?</p>	<p>Yes: Pass to RPh. Deny; medical appropriateness</p>	<p>No: Go to #14</p>
<p>14. Is the prescribed product a buprenorphine monotherapy product (i.e., without naloxone)</p>	<p>Yes: Go to #15</p>	<p>No: Go to #176</p>
<p>15. Is the patient pregnant or a female actively trying to conceive?</p>	<p>Yes: Go to #17</p>	<p>No: Go to #16</p>
<p>16. Does the patient have a contraindication or intolerance to buprenorphine/naloxone combination products that prevents successful management of opioid use disorder?</p>	<p>Yes: Go to #17</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>

Approval Criteria

17. What is the expected length of treatment?

Document length of therapy: _____

Approve for anticipated length of treatment or 6 months, whichever is shorter.

Table 1. Criteria for Approved Use of Probuphine (buprenorphine implant).¹

<p>PROBUPHINE implants are only for use in patients who meet ALL of the following criteria:</p> <ul style="list-style-type: none"> • Patients should not be tapered to a lower dose for the sole purpose of transitioning to PROBUPHINE • Stable transmucosal buprenorphine dose (of 8 mg per day or less of a sublingual Subutex or Suboxone sublingual tablet or its transmucosal buprenorphine product equivalent) for 3 months or longer without any need for supplemental dosing or adjustments: <ul style="list-style-type: none"> ○ Examples of acceptable daily doses of transmucosal buprenorphine include: <ul style="list-style-type: none"> ▪ Subutex (buprenorphine) sublingual tablet (generic equivalent) 8 mg or less ▪ Suboxone (buprenorphine and naloxone) sublingual tablet (generic equivalent) 8 mg/2 mg or less ▪ Bunavail (buprenorphine and naloxone) buccal film 4.2 mg/0.7 mg or less ▪ Zubsolv (buprenorphine and naloxone) sublingual tablets 5.7 mg/1.4 mg or less 	
<p>Consider the following factors in determining clinical stability and suitability for PROBUPHINE treatment:</p> <ul style="list-style-type: none"> • no reported illicit opioid use • low to no desire/need to use illicit opioids • no reports of significant withdrawal symptoms • stable living environment • participation in a structured activity/job that contributes to the community • consistent participation in recommended cognitive behavioral therapy/peer support program • stability of living environment • participation in a structured activity/job 	
<p>Reference: PROBUPHINE (buprenorphine implant for subdermal administration) [Prescribing Information]. Princeton, NJ: Braeburn Pharmaceuticals, Inc., May 2016.</p>	

Renewal Criteria

1. Has the patient been assessed for the effectiveness of the treatment plan and overall progress that warrants continued treatment with buprenorphine?

Yes: Go to # 2.

No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
<p><u>2. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com), and has the prescriber verified evaluated the PDMP at least once in the past 6 months, and verified that the patient is not currently has not been prescribed any opioid analgesics from other prescribers?</u></p>	<p><u>Yes: Go to #3</u></p>	<p><u>No: Pass to RPh. Deny; medical appropriateness</u></p>
<p><u>3. Does the patient have a contraindication or intolerance to buprenorphine/naloxone combination products that prevents successful management of opioid use disorder?</u></p>	<p><u>Yes: Go to # 4</u></p>	<p><u>No: Pass to RPh. Deny; medical appropriateness</u></p>
<p><u>2-4.</u> What is the expected length of treatment?</p>	<p>Document length of therapy: _____ Approve for anticipated length of treatment or 6 months, whichever is shorter.</p>	

P&T/DUR Review: 11/18 (DM); 1/17; 9/16; 1/15; 9/09; 5/09
 Implementation: TBD; 4/1/2017; 9/1/13; 1/1/10