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OPIOID USE DISORDER TREATMENT WITH SUBLOCADE

Drug Regimen Review Center

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Introduction

Treatment advancement for opioid use disorder is paramount, as opioid-related mortality rates overshadow recovery. Opioid abuse is associated with adverse sequelae including premature death, and has significant medical, societal, and criminal-justice costs.[1] In addition to implementing prevention measures, healthcare allies continue to address the gap(s) in care when it comes to treating opioid use disorder (OUD). The Surgeon General's 2016 report highlighted that "[o]nly about 10 percent of people with a substance use disorder receive any type of specialty treatment."[2]

The most widely used pharmacotherapies for OUD are methadone and buprenorphine-containing products. These are controlled substances that are more highly regulated compared to the opioid antagonist option, naltrexone. Treatment with buprenorphine, a Schedule III controlled substance, can be carried out via an office-based setting by a waivered physician (per the Drug Addiction Treatment Act of 2000).[3] Patients can have oral buprenorphine prescriptions dispensed to them at retail pharmacies; however, without observed-dosing oversight, this dosage form may be diverted[4-6] and has been involved in accidental pediatric exposures.[7,8] Methadone, a Schedule II controlled substance, is prescribed and dispensed for OUD only in a highly-structured opioid therapy program (OTP), licensed by the United States Substance Abuse and Mental Health Services Administration (SAMHSA).[9] Longer-acting formulations of both buprenorphine and naltrexone have been developed to improve adherence.

This report reviews the appropriate use of the recently approved extended-release (ER) buprenorphine depot product, Sublocade, and factors that may affect efficacy and safety outcomes with its use. Sublocade was granted a priority review status, as the FDA considered that the depot formulation could potentially improve certain safety issues related to buprenorphine transmucosal products—namely, the risk of abuse, drug diversion, and accidental pediatric exposure associated with buprenorphine take-home supplies.[10]

The Utah Medicaid Preferred Drug List (PDL) currently includes Suboxone, Vivitrol, and generic naltrexone tablets as preferred options in the OUD treatment category. Non-preferred products include Bunavail, Sublocade, Zubsolv, generic buprenorphine/naloxone, and generic buprenorphine. The PDL notes that both Sublocade and Vivitrol require direct dispensing to the provider. In addition, Utah Medicaid has developed prior authorization criteria for all buprenorphine-containing oral products used for OUD. Buprenorphine products were last reviewed by the DUR Board in November 2016 and by the Pharmacy and Therapeutics Board in September of 2017.

Methodology— A literature search for systematic reviews was conducted in the Cochrane Library and Medline (PubMed). The FDA website, the SAMHSA website, and the National Guideline Clearinghouse (www.guideline.gov) were searched for safety information, clinical trials, and treatment guidelines. Relevant information from the following reports,

prepared by the University of Utah's Drug Regimen Review Center, was incorporated into this document: *Drug Class Reviews, Opioid Dependence Treatment With Buprenorphine: November 2016; Opioid Dependence Treatment with Vivitrol: April 2017*; and *Agents for the Treatment of Opioid Use Disorder: September 2017.*

Sublocade (Buprenorphine ER, Subcutaneous Depot) for Opioid Use Disorder

I. Opioid Use Disorder Overview

Abuse of opioids is associated with serious infections (e.g. hepatitis C virus, human immunodeficiency virus, and endocarditis) secondary to intravenous illicit use, and premature death regardless of the route of administration.[1,11] For 2016, the Utah opioid-overdose death rate was reported by the Center for Disease Control and Prevention (CDC) to be 16.4 per 100,000 population (466 total cases).[12] Sixty-five percent of the opioid-overdose cases in Utah, during 2012 to 2014, occurred in individuals with a known substance abuse disorder.[13] Other co-occurring circumstances included physical health (61%) and mental health (56%) disorders, alcohol dependence (16%), and a history of suicide attempts (10%).[13]

Regional-level data shows opioid-overdose emergency-department visits increased by 40.3% in the west region of the US, from July 2016 to September 2017.[14] Illicitly manufactured fentanyl and its analogs were the primary drivers of the five-fold increase in the national prevalence of synthetic-opioid overdoses from 2013 through 2016.[15]

In response to the opioid-abuse crisis, in April 2017, the U.S Department of Health & Human Services (HHS) announced its initiatives to spur judicious opioid prescribing practices, reduce the public burden of OUD and overdose, and expand naloxone access and medication-assisted treatment for underserved populations.[16] Federal funding through A State Targeted Response to the Opioid Crisis Grants (Opioid-STR) has been established to help implement the HHS initiatives; Utah qualified for a 2-year grant in 2017.[17]

Preventative strategies such as the Utah Controlled Substance Database Program, which provides prescribers and pharmacists with opioid-prescription fill histories, are implemented to curb inappropriate prescribing. Federal and state-level guidelines have also been published to influence opioid prescribing.[18,19] In recent years, opioid prescribing in Utah has declined from 82.1 per 100 persons in 2013 to 70.4 per 100 persons in 2016;[20] 2017 data is not yet available. This shows a change from the previous trend when the Utah rate of prescription-opioid dispensing increased by 29% from 2002 to 2015.[18,21]

Opioid use disorder, formerly known as opioid dependence, is the diagnosis term used in the current 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which combines the "opioid abuse" and "opioid dependence" criteria from previous DSM versions.[9] Treatment of OUD is challenging and often progresses as a series of remissions and relapses.[22] Woody et al explain that "[s]ustained remission occurs in a

significant minority of individuals, but it usually takes 10 or more years to emerge, and many survivors have medical and psychosocial problems that permanently impair their health, chances for employment, and overall adjustment."[22] Opioid use disorder is conceptualized as a chronic, relapsing disease[9,23-25] that involves managing patients through opioid withdrawal, induction, and maintenance stages, with many needing long-term treatment and/or requiring multiple treatment episodes.[25] A paired pharmacological-psychosocial treatment approach has improved outcomes in both the detoxification and maintenance stages.[9] Many factors including patient attitudes[26,27] and access to care (i.e. transportation, appointment availability) influence the chosen treatment and retention outcome.[28]

The National Institute on Drug Abuse highlights that a relapse episode signals a need for adjustment to the patient's therapy, or a re-initiation of therapy— all while remaining cognizant of a person's changing needs.[25] The prescriber should also continuously monitor the patient's drug use,[25] for instance with urine drug screening, unit-dose counting, available state controlled-substance prescribing databases, and patient-reported adherence.

II. Sublocade (Buprenorphine ER, Subcutaneous Depot)

Buprenorphine is a mixed opioid agonist-antagonist with affinity for the mu-opioid receptor; it is also a kappa-opioid receptor antagonist.[29] The long-acting Sublocade product utilizes an Atrigel delivery system, in which a drug-polymer solution containing buprenorphine is injected subcutaneously and solidifies into a semi-solid depot upon contact with body fluids. This delivery system facilitates a once-a-month administration frequency.

Sublocade is licensed for use as part of a comprehensive OUD management program. Candidates for Sublocade are patients who have already initiated and achieved stability on a transmucosal-buprenorphine product at 8 to 24 mg per day for at least 7 days preceding initiation of the depot.[30] The depot product is available in two strengths (100 mg and 300 mg per depot) and must be administered subcutaneously into the abdominal area by a trained healthcare professional.[30] Sublocade dosing is initiated at 300 mg monthly for two months, followed by monthly 100 mg maintenance doses. Based on clinical response, the maintenance dose may be increased back to 300 mg/month if needed.

The package labeling recommends assessing liver function at baseline and periodically throughout treatment. Although the impact of hepatic impairment has not been studied with the depot formulation, information from a pharmacokinetic study with buprenorphine/naloxone 2 mg/0.5 mg sublingual tablets found that patients with moderate to severe hepatic impairment had a 64% and 181% increase in exposure, respectively.[10] The FDA-approved labeling for Sublocade notes that patients with pre-

existing moderate to severe hepatic impairment are not candidates for buprenorphine depot therapy.

The manufacturer has developed a Risk Evaluation and Mitigation Strategy (REMS) Program to educate prescribers about the administration and direct-to-provider dispensing requirements, in order to avoid detrimental effects of intravenous self-administration by a patient (a black-box warning). Materials included as part of the program are a Healthcare Setting and Pharmacy Enrollment Form (for certification of providers), a Dear Healthcare Provider REMS Letter, a Fact Sheet, and the REMS Program website through which certification for provision of the drug can be obtained (www.sublocaderems.com).[10] Certified healthcare settings and pharmacies must detail their established procedures to meet the dispensing requirements.

Pharmacokinetics— The buprenorphine peak plasma concentration is reached at 24 hours post injection.[29] The concentration then declines to a plateau as the polymer matrix slowly biodegrades. Steady-state occurs between 4 and 6 months with monthly injections.

The metabolism of buprenorphine is dependent on cytochrome P450 3A4 (CYP3A4); thus, strong CYP3A4 inhibitors (e.g. azole antifungals, erythromycin, ritonavir) or inducers (e.g. rifampin, carbamazepine, phenytoin) may affect buprenorphine plasma levels, efficacy, and the potential for adverse events. Buprenorphine also inhibits CYP2D6 and CYP3A4; however, the product labeling notes that the plasma concentrations of buprenorphine are not expected to affect the metabolism of other concomitant medications to any significant degree.[29]

The slow release system yields a long terminal half-life of 43 to 60 days.[29] Approximately 30% of the buprenorphine dose is excreted through the urine, primarily as metabolites and < 1% as unchanged drug.[10] Nearly 70% of the dose is excreted through the feces, 33% of this portion as unchanged drug and the remainder as metabolites. Once steady-state is achieved, buprenorphine remains detectable in the plasma for twelve months or longer following therapy discontinuation.[29]

Table 1 provides prescribing information from the FDA-approved product labeling.

Table 1. Sublocade Prescribing Information: Indications, Dosing, and Use Concerns [30]

Dosage Form and Storage	**Sublocade (buprenorphine extended-release):** prefilled syringes for single use ▪ Strengths: 100 mg/0.5 mL and 300 mg/1.5 mL ▪ Refrigerate (35.6 to 46.4°F); may be unrefrigerated (59 to 86°F) for up to 7 days
FDA Approved Indications	▪ Should be used as part of a comprehensive management program that includes counseling and psychosocial support ▪ Approved for 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.
Dosage and Administration	**Dose:** Following induction with a buprenorphine-transmucosal product delivering the equivalent of 8 to 24 mg of buprenorphine daily for a minimum of 7 days, initiate Sublocade 300 mg subcutaneously, once monthly, for the first two months followed by maintenance

Table 1. Sublocade Prescribing Information: Indications, Dosing, and Use Concerns [30]

	dosing of 100 mg monthly. The maintenance dose may be increased to 300 mg monthly for patients who tolerate the 100 mg dose but who have inadequate clinical response based on self-reported illicit opioid use or urine drug screening. **Hepatic Dysfunction:** Patients with pre-existing moderate to severe hepatic impairment are not candidates for treatment **Administered** as an abdominal, subcutaneous injection at monthly intervals with a minimum of 26 days between doses ▪ A healthcare provider must prepare and administer the medication per the product labeling using only the syringe and safety needle included with the product ▪ Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.
Monitoring	▪ Liver function testing should be performed at baseline and during treatment at monthly intervals (especially with the 300 mg monthly dosage) ▪ Periodically reassess the need for continuing medication-assisted therapy ▪ Should examine injection site for signs of infection or evidence of tampering. Monitor patients for symptoms of withdrawal for several months after initiation.
Inappropriate Use	**Black-box Warning:** Avoid intravenous administration, which can lead to intravascular occlusion, serious, harm, and death. A Risk Evaluation and Mitigation Strategy program is set up to ensure the drug is dispensed directly to a healthcare provider who is properly trained. **Contraindicated** in patients with hypersensitivity to buprenorphine or the ATRIGEL delivery system

III. Place in Therapy

The CDC and the Utah Medical Association have each published guidelines for opioid prescribing that recommend prescribers offer or arrange evidence-based pharmacotherapy in combination with behavioral therapy for patients with OUD.[18,31] The most widely used pharmacotherapies for OUD are methadone (a full-opioid agonist) and buprenorphine (BUP) products. Issues involved with these agents include physical dependence, risk for diversion risk,[4-6,32] and additive respiratory depression risk with other central nervous system (CNS) depressants.[7,33,34] Nonetheless, "[s]tudies have shown that they are most effective when used over an extended, but as-yet-unspecified, period of time and with counseling and other services..."[22] Naltrexone, an opioid antagonist option, is not associated with physical dependence, diversion, or additive CNS depression. The daily-dosed oral formulation of naltrexone, however, has a long-standing history of poor compliance[35] and high drop-out rates.[36]

Until 2016, buprenorphine for OUD was only available in the US as oral formulations. Naloxone, an opioid antagonist is incorporated into oral buprenorphine formulations to reduce abuse potential. Longer-acting formulations of both buprenorphine and naltrexone have been developed to help improve adherence and limit diversion and abuse associated with oral buprenorphine:

a) Extended-release (XR) naltrexone intramuscular injection (Vivitrol) was approved for OUD in 2010. The product was initially FDA approved for the treatment of alcohol dependence in 2006

b) Buprenorphine implant (Probuphine) was FDA-approved for OUD in May of 2016

c) Buprenorphine extended-release subcutaneous depot was FDA approved for OUD in November of 2017

Naltrexone XR is administered monthly and can be initiated only after the patient has been opioid-free for at least 7-10 days, which may be intolerable for some patients.[30] Naltrexone XR is also indicated for alcohol dependence;[30] whereas, buprenorphine products do not have this additional indication. The buprenorphine implant (Probuphine) provides constant low-level exposure for 6 months and is indicated for patients who have achieved clinical stability on ≤8 mg of buprenorphine daily equivalents of a short-acting buprenorphine product.[37] Probuphine requires surgical insertion and removal, and carries a risk of implant migration.[37]

The buprenorphine depot product, Sublocade, is administered more frequently, on a monthly basis, compared to the implant formulation which is administered every 6 months. The buprenorphine depot also allows for a higher range of the transmucosal buprenorphine lead-in dose (8 to 24 mg equivalents of buprenorphine) compared to the allowable lead-in dose for Probuphine (≤8 mg equivalents of buprenorphine).

In the FDA drug summary review, the reviewer commented that there were no head-to-head studies of Sublocade versus other buprenorphine products, but theoretical advantages of this product include (a) a monthly injection frequency to which patients may be more adherent compared to daily dosed BUP regimens, and (b) less risk of misuse, abuse, diversion, and accidental overdose associated with providing take-home-doses of a controlled substance.[10]

Table 2 provides a list of the available buprenorphine-containing products approved for OUD management. Summary information for agents indicated for OUD in the United States is included in **Appendix A**, Table 1.

Table 2. Buprenorphine-Containing Products Indicated for Opioid Use Disorder

Product	*Route*	*Strengths Available*
Short Acting Buprenorphine Products		
Buprenorphine Single-Ingredient Product		
Generic of Subutex (DSC) Tablet	Sublingual	2 mg; and 8 mg
Buprenorphine/Naloxone Combination Products		
Bunavail Film	Buccal	2.1 mg/ 0.3 mg; 4.2 mg /0.7 mg; and 6.3 mg/ 1 mg
Suboxone Film	Sublingual	2 mg/ 0.5 mg; 4 mg/ 1 mg; 8 mg/ 12 mg; and 12 mg/3 mg
Generic of Suboxone (DSC) Tablet	Sublingual	2 mg/ 0.5 mg; and 8 mg/ 2mg
Zubsolv Tablet	Sublingual	0.7 mg/ 0.18 mg; 1.4 mg/ 0.36 mg; 2.9 mg/ 0.71 mg; 5.7 mg/1.4 mg; and 8.6 mg/ 2.1 mg; 11.4 mg/ 2.9 mg
Long Acting Buprenorphine Products		
Buprenorphine Single-Ingredient Products		
Sublocade Depot	Subcutaneous	100 mg/ 0.5mL; and 300 mg/1.5 mL
Probuphine Implant	Subdermal	80 mg/ implant

Abbreviation: DSC, brand product discontinued

Clinical Guidelines—The 2015 American Society of Addiction Medicine (ASAM) treatment guideline recommends individualized therapy. For patients who are candidates for take-home supplies of oral buprenorphine maintenance therapy, the authors recommend that a BUP/naloxone-combination formulation be used, except for pregnant women for whom the buprenorphine mono-product is preferred.

For non-pregnant patients, the 2015 Department of Veterans Affairs and Department of Defense (VA/DoD) guideline concludes that there is strong evidence supporting opioid agonist therapy and moderate evidence supporting extended-release naltrexone (XR-NTX) for relapse prevention;[38] therefore, methadone and buprenorphine-naloxone products are designated as first-line agents. XR-NTX is a second-line option for patients unwilling to take, or whom have failed opioid-agonist therapy; patients with contraindications; or individuals without access to preferred options. The 2011 recommendations of the World Federation of Societies of Biological Psychiatry are similar.[38,39] At the time of publication of these three guidelines, long-acting buprenorphine products were not yet on the market.

Selection of the appropriate regimen and treatment venue should be guided by the patient's disease history and preferences, the provider's assessment of the patient's psychosocial situation, co-occurring disorders, opportunities for treatment retention, and risk of medication diversion.[9,38-40] The ASAM practice guideline summarizes that the goals

of buprenorphine treatment are to suppress opioid withdrawal, antagonize the effects of opioid intake, stop or reduce the use of illicit opioids, reduce opioid cravings, and promote patient engagement in other recovery strategies. The guideline advises employing buprenorphine therapies with caution in patients using alcohol, sedatives, hypnotics, or anxiolytics, via more intensive monitoring or by moving a patient to an OTP setting with greater supervision.[9]

Treatment with buprenorphine involves an induction phase, stabilization phase, and maintenance phase. Upon discontinuation of full opioid agonists, patients are generally initiated onto buprenorphine when they begin experiencing mild to moderate opioid withdrawal symptoms (approximately 6 to 12 hours after the last short-acting opioid dose, or 24 to 72 hours after the last long-acting opioid dose).[9] The provider titrates buprenorphine to the minimum dosage needed to prevent withdrawal symptoms and reduce cravings while tailoring treatment to the type of opioid dependence— short-acting opioid dependence versus long-acting opioid dependence. The stabilization phase occurs as the patient no longer experiences withdrawal symptoms. The ASAM guideline does not recommend specific treatment durations regarding each agent; however, it highlights that relapse rates are high for most patients. Thus, long-term treatment is often needed and should be decided based on the prescriber's assessment of both the patient's response and circumstances.[9] A similar recommendation is made by other authors.[25,38] Optimal maintenance dosing of buprenorphine regimens will vary from patient to patient.

Patients that *may be* more suitable candidates for the buprenorphine depot over methadone or buprenorphine-containing oral products are those who have difficulty adhering to more frequent dosing regimens of methadone or buprenorphine (e.g. patients with concomitant psychiatric diagnoses that impair their ability to maintain daily attendance at a methadone treatment center or to take their daily prescription consistently) or where diversion is a concern.

Table 3 provides an overview of the treatment guidelines for OUD pharmacotherapy published within the last 5 years.

Table 3. Clinical Guidelines

Clinical Guideline	Recommendations
The ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use; 2015 [41,42]	**Treatment Options for Opioid Use Disorder**- Clinicians should consider the patient's preferences, past treatment history, psychosocial situation, co-occurring disorders, and risk of diversion when deciding between the treatment venue and the medication (e.g. methadone, buprenorphine, and naltrexone) o Use of other addictive drugs (i.e. marijuana, stimulants) should not be a reason to suspend opioid use disorder treatment, although, these types of patients have been shown to have poorer outcomes. o The use of benzodiazepines and other sedative hypnotics may be a reason to suspend agonist treatment because of safety concerns related to respiratory depression and opioid agonists o The venue in which treatment is provided is as important as the specific medication selected. o Opioid Treatment Program (OTP): patients may benefit from this daily supervised setting o Office based opioid treatment may not be suitable for patients with active alcohol use disorder or sedative, hypnotic, or anxiolytic use disorder (or who are in the treatment of addiction involving the use of alcohol or other sedative drugs, including benzodiazepines or benzodiazepine receptor agonists). o Addiction should be considered a bio-psycho-social-spiritual illness, for which the use of medication(s) is but only one component of overall treatment. **A.** Methadone (opioid agonist): recommended for patients who may benefit from supervised daily dosing in an OTP, or for patients for whom failed buprenorphine **B.** Naltrexone (opioid antagonist): poor outcomes are often observed as a result of poor medication adherence to the oral dosage form, however, may be considered for patients in whom adherence can be supervised or enforced. The extended-release naltrexone injectable product may be more appropriate for those with adherence issues. Extended-release injectable naltrexone: reduces, but does not eliminate, issues with medication adherence. **C.** Buprenorphine (partial opioid agonist): The combination product (BUP/NLX) is recommended for withdrawal management and treatment of OUD, however the BUP mono-product is recommended for use during pregnancy. **Special Populations** (refer to guideline for additional information) • *Pregnant women*- Use methadone or buprenorphine mono-product; If taking naltrexone prior to becoming pregnant, the decision to discontinue the medication (if relapse risk is low) or to continue naltrexone are options; however, informed consent of the reviewed risks should be documented. • *Adolescents*- Although FDA approval of these agents is limited in regard to patients under age 18, the guideline advocates that practitioners should consider employing pharmacotherapy for adolescents with OUD. • *Individuals in the Criminal Justice System*- Treatment with naltrexone XR is recommended; oral naltrexone is not recommended. • *Patients with Pain*-Treat mild pain with NSAIDs and moderate to severe pain with short-term use of ketorolac. • *Surgery:* Naltrexone XR should be discontinued 30 days prior to surgery

Table 3. Clinical Guidelines

Clinical Guideline	Recommendations

VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders; 2015 [38]	**Pharmacotherapy for Opioid Use Disorder**
	• The following medications are recommended, with consideration of patient preferences
	  o Buprenorphine/naloxone combination therapy
	  o Methadone in an opioid treatment program
	• The appropriate treatment setting should be individualized with consideration of patient preferences
	• For patients who are unwilling, have contraindications, or do not have accessibility to opioid agonist therapy, and who have been opioid free for a sufficient period of time, a prescriber shall offer extended-release injectable naltrexone
	• There is insufficient evidence to recommend for or against oral naltrexone for treatment of opioid use disorder.
	Psychosocial Interventions
	• For patients receiving office-based buprenorphine treatment, there is insufficient evidence to recommend for or against any specific psychosocial intervention. The choice of psychosocial intervention should be made considering patient preferences and provider training/competence.
	• In opioid treatment program settings, patients should be offered individual counseling and/or contingency management, considering patient preferences and provider training/competence.

Abbreviation key: ASAM, American Society of Addiction Medicine; BUP, buprenorphine; NSAIDs, non-steroidal anti-inflammatory drugs; NLX, naloxone; OBOT, office-based opioid treatment; OTP, opioid treatment program; OUD, opioid use disorder; XR, extended-release

Efficacy

No systematic reviews were identified pertaining specifically to the depot formulation of buprenorphine. Evidence supporting the efficacy of the buprenorphine depot includes a 24-week, randomized, placebo-controlled, phase 3 trial. Results from this unpublished study were found in grey literature sources including clinicaltrials.gov and from the FDA drug-application materials. Prospective, randomized studies have not been published that directly compare Sublocade to any other buprenorphine formulation, methadone, or naltrexone dosage form to contrast possible treatment-effect differences between OUD therapy options.

Phase 3, Randomized, Double-blind, Controlled Trial (ClinicalTrials.gov Identifier, NCT02357901) — Eligible patients for randomization were those who underwent a run-in phase where they were initiated and stabilized onto Suboxone films. Patients had to have minimal opioid craving symptoms (with a score of ≤ 20 mm on the Opioid Craving Visual Analog Scale), or withdrawal (with a score of ≤ 12 on the Clinical Opiate Withdrawal Scale) after at least 7 days on the sublingual film.[10]

Patients were then randomized to 2 dosing regimens of the buprenorphine depot and matching placebo arms, for a total of 6 monthly doses: (a) 300 mg monthly for 6 months, abbreviated 300/300 mg, or (b) 300 mg monthly for 2 months, then 100 mg monthly for 4 months, abbreviated 300/100 mg. Response was assessed at week 5 and then weekly through week 24. Each group also received drug/behavior counselling at least once per week.[10] Both regimens were superior to placebo for the primary endpoint which was the cumulative distribution function of drug-use assessments (accounting for the percentage of opioid-negative urine samples combined with self-reports negative for opioid use) from week 5 through week 24 (Wilcoxon rank-sum test for superiority, $P<0.001$).[10]

Superiority to placebo was also demonstrated for the following secondary endpoints, among others:

- Percentage of participants considered a treatment success, defined as having ≥80% negative urine samples for opioids combined with self-reports of no illicit opioid use from Week 5 through Week 24 (29% of patients in the 300/300 mg group and 28% of patients in the 300/100 mg group compared to 2% of patients in the placebo group)[43]
- Proportion of 100% negative drug-use assessments (13% of patients in the 300/300 mg group and 12% of patients in the 300/100 mg group compared to 1% of patients in the placebo group)[10]
- Percentage of participants who were abstinent at week 24, defined as both a negative urine sample and self-reported opioid use (44% of patients in the 300/300 mg group and 37% of patients in the 300/100 mg group compared to 2% of patients in the placebo group)[43]

Safety

Adverse reactions occurring in at least 2% of the patients receiving the buprenorphine depot in the phase 3 double-blind study included gastrointestinal related disorders (e.g. constipation, nausea, and vomiting), fatigue, and nervous system disorders (e.g. headache, sedation, somnolence).[29] Elevations of liver enzymes, creatine phosphokinase, and gamma-glutamyl transferase were additionally reported; though, no cases of serious liver injury were associated with Sublocade use. Dose-dependent reactions that occurred more frequently in the higher dosage regimen (300/300 mg) compared to the lower dosage regimen (300/100 mg) included treatment-emergent drug discontinuation, injection site reactions, and liver enzyme elevations.[29]

Injection site reactions occurred in approximately 16% of patients receiving the study drug in the phase 3 RCT, compared to 9% of the placebo group. The most common reactions were injection site pain, pruritus, and erythema.

Safety limitations— There is limited possibility of removing the depot. Some of the depot contents may be extractable during the 2 weeks following the injection; nonetheless, a patient may have residual effects from previous injections or from only partial removal.[10] A patient who does not tolerate the medication will require long-term monitoring by a health care professional.

Postmarketing studies aim to define (a) specific populations that may benefit from the 300 mg monthly regimen over a 100 mg monthly regimen, (b) assess whether patients having long-term stability on a transmucosal buprenorphine can forego the 300 mg loading doses before receiving the 100 mg dosage, and (c) determine whether patients can initiate the depot without the initial 7 day-minimum run-in on transmucosal buprenorphine.[10]

Table 4 provides a summary of the labeling information regarding general warnings, recommended precautions, and concerns regarding special populations.

Table 4. Safety Concerns for Buprenorphine Depot[30]

Special Populations[a]	**Pregnancy-** use during pregnancy only if the potential benefit justifies the potential risk to the fetus
	Lactation- buprenorphine passes into the mother's milk, so increased risk cannot be ruled out; monitor the infant for increased drowsiness and breathing difficulties
	Geriatric Patients- monitor patients for sedation or respiratory depression while considering possible decreased hepatic, renal, or cardiac function
	Moderate to Severe Hepatic Impairment- use is not recommended
	Pediatric Use- safety and efficacy have not been established

Table 4. Safety Concerns for Buprenorphine Depot[30]

Warnings and Precautions[a]	Not for use in **opioid naive individuals** **Addiction, Abuse, and Misuse**- Monitor patients for diversion or progression of opioid addictive behaviors **Respiratory Depression**- Warn patients of the potential danger of severe respiratory depression with the concomitant use of benzodiazepines or other CNS depressants. Use with caution in patients with compromised respiratory function (e.g. COPD, decreased respiratory reserve, hypoxia, etc.) **Manage Risks from Concomitant Use of Benzodiazepine or other CNS Depressants and Ensure Coordination of Care** • Preferred- gradual tapper off of benzodiazepines or other CNS depressants OR • Monitor at a higher level of care while tapering OR • Decrease benzodiazepines or other CNS depressants to the lowest effective dose For patients in buprenorphine treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Toxicology screening should test for prescribed and illicit benzodiazepines **Neonatal Opioid Withdrawal Syndrome (NOWS)**- NOWS is an expected and treatable outcome of chronic opioid use during pregnancy **Adrenal Insufficiency**: Teat with corticosteroids and wean patient off opioid if they experience adrenal insufficiency **Risk of Opioid Withdrawal with Abrupt Discontinuation**- Upon discontinuing Sublocade, monitor patients for several months. Withdrawal syndrome from buprenorphine is milder than that seen with full agonists and may be delayed in onset. Consider transmucosal buprenorphine to treat withdrawal • Plasma concentrations following steady-state via buprenorphine depot decrease slowly over time following the last injection and can remain at therapeutic levels for 2 to 5 months **Risk of Hepatitis, Hepatic Events**- Monitor liver function at baseline and for possible elevations during treatment **Risk of Withdrawal in Patients Dependent on Full Agonist Opioids**- Patient must be clinically stable on transmucosal BUP before initiating Sublocade **Treatment of Emergent Acute Pain**- If possible acute pain should be treated with a non-opioid analgesic. If an opioid is required, patients should be monitored closely **Use in Patients at Risk for Arrhythmia**- Buprenorphine has been observed to prolong the QTc interval in some patients participating in clinical trials. Avoid the use of buprenorphine in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval **Impairment of Ability to Drive or Operate Machinery**- Caution patients about driving or operating hazardous machinery until they are reasonably certain that Sublocade does not adversely affect their ability to engage in such activities **Orthostatic Hypotension**- use with caution

[a] Additional information can be found in the product's prescribing information.
Abbreviations: AUC, area under the curve; CrCl, creatinine clearance; OUD, opioid use disorder; RCTs, randomized controlled trials

Medicaid Utilization Data

Table 5. Sublocade (Buprenorphine Extended-Release Depot) Utilization; ACO + FFS, May 2017 through April 2018

Claims (patient) counts	Query for ICD10 diagnosis codes[a] F1120, F1121, F1123
• **<5 (<5)** • All claims were attributed to the adult population	• Patient(s) had at least one of the above ICD10 diagnosis codes

[a] ICD10 Codes: F1120, Opioid dependence, uncomplicated; F1121, Opioid dependence, in remission; F1123, Opioid dependence with withdrawal

Potential Prior Authorization Criteria and Discussion Topics

The following items may be considered for developing prior authorization criteria regarding Sublocade, buprenorphine depot injection therapy:

- Documented diagnosis corresponding to the FDA-approved indication: moderate to severe OUD (Sublocade is not indicated or approved for pain treatment)
    - Opioid naïve patients are not candidates for treatment. Product labeling includes case reports of deaths in opioid naïve individuals following a 2 mg dose of buprenorphine sublingual tablet. The depot dosage form provides high systemic buprenorphine exposure.
- Documentation that patients have recently initiated a transmucosal buprenorphine product, AND have achieved clinical stability on an 8 to 24 mg daily dose for at least 7 days prior to switching to the depot formulation
- An injection frequency limit of once monthly, with a minimum of 26 days in-between administrations
- Requirement for direct dispensing to the provider for subcutaneous administration by the provider
- Documentation of investigation of urine analysis for illicit or inappropriate drug use, as ongoing opioid use could impact the lead-in phase
- Documentation of liver function testing at baseline and during therapy as specified in the package insert

Other considerations

- Exclude patients with pre-existing moderate to severe hepatic impairment. These patients are not treatment candidates per product labeling.
- Dosing should be congruent with FDA-approved labeling
- Ongoing illicit drug use monitoring (i.e. per urine analysis, check with Utah Controlled Substance Database, and patient reporting)

- During the lead-in phase, require that the patient is not taking other prescribed opioids, other than a transmucosal buprenorphine product (prescribers can affirm that they have conducted a review of the patient's profile on the state's controlled-substance prescription database for any potentially unreported use)
- Proof of the provider's certification upon completing the REMS program established for this product
- Consider adding recommendations to coordinate care with providers prescribing CNS-depressants. Dose adjustment of other medications (e.g. benzodiazepines, muscle relaxers, or other CNS depressants) may be warranted, especially for those with compromised respiratory function. The following quote from the package labeling can be added to the PA-criteria document for added emphasis.

  "For patients in buprenorphine treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's buprenorphine treatment and coordinate care to minimize the risks associated with concomitant use."[29]

Special Populations

- *Pregnancy*: The American College of Obstetricians and Gynecologists (ACOG) concluded in 2012, that the available evidence "supports the use of buprenorphine as a potential first-line medication for pregnant opioid-dependent women who are new to treatment."[44] Other authors assert that methadone remains the standard treatment because of the lack of data on pregnancy outcomes after first trimester buprenorphine exposure, and the lack of data on long-term neurodevelopmental outcomes after in utero exposure.[44] Currently, there is inadequate data assessing the use of buprenorphine depot during pregnancy. Product labeling advises that it should be used only if the benefits clearly outweigh the risks.
- *Pediatric Use*: Sublocade safety and efficacy has not been established in the pediatric population for OUD management. Furthermore, the pharmacokinetics and dosing has not been established in this population. Nonetheless, the ASAM (American Society of Addiction Medicine) guideline authors advise that practitioners should consider all available pharmacotherapies for the adolescent OUD population.[9]

Supportive Counseling— Efficacy of the depot product was demonstrated when used as part of a treatment program that included counseling and psychosocial support. Nonetheless, potential barriers to OUD treatment access that could be relevant to our population may include requirements for concurrent counseling aimed at improving adherence, but that could deter patients from initiating or continuing treatment if not easily accessible.[45]

Summary

Sublocade is a long-acting buprenorphine formulation that offers a once-monthly dosing frequency for the treatment of opioid use disorder. It is appropriate patients who have been stabilized on an 8 to 24 mg/day buprenorphine dose equivalent of a transmucosal product. This allowable run-in dose range is higher than what is appropriate for Probuphine initiation—the buprenorphine extended-release implant for patients who have achieved clinical stability on 8 daily mg equivalents of buprenorphine or less during the run-in phase. There are no published head-to-head studies that compare Sublocade to any other buprenorphine formulation, methadone, or naltrexone dosage form to contrast possible treatment-effect differences between OUD therapy options. Thus, treatment-effect differences between Sublocade and other formulation of buprenorphine remains unclear.

Planned postmarketing studies will include an evaluation of subpopulations that may benefit from the higher Sublocade 300 mg monthly regimen versus a 100 mg maintenance dose, and will assess if certain individuals can forgo the lead-in transmucosal buprenorphine phase or the two 300 mg Sublocade loading doses.

Potential prescribing criteria are outlined for discussion on page 15, while keeping in mind that a long-acting product may be especially useful for patients who have failed long-term therapy with other options, or where diversion of buprenorphine take-home products may be a concern.

Appendix A

Table 1. Comparison of Maintenance Treatment Options for OUD[11,42,46-55]

	Methadone	***Buprenorphine Pill or film***	***Buprenorphine Implant***	***Extended Release Naltrexone***	***Oral Naltrexone***
MOA	Full mu-opioid receptor agonist	Partial mu-opioid receptor agonist		Full mu-opioid receptor antagonist	
Pharmacokinetics	• Highly variable inter-individual pharmacokinetics • Long bi-phasic half-life with high potential for accumulation: ⇨ delayed toxicity including respiratory depression ⇨ may take up to 10 days to reach steady-state serum levels.	• Significant first-pass metabolism, but high lipid solubility so excellent sublingual bioavailability • Both buprenorphine and naloxone are extensively metabolized by liver		• Avoids first-pass metabolism, so overall therapy involves a lower total daily dose than oral-NTX, however, the steady state AUC is higher compared to oral therapy • Not metabolized by CYP enzymes, however is excreted primarily as its metabolite through the urine.	• Significant first-pass metabolism • Not metabolized by CYP enzymes, however is excreted primarily as its metabolite through the urine.
DEA Schedule	Yes: CII	Yes: CIII		No	
Indication	• Detoxification & maintenance treatment of opioid addiction, in conjunction with appropriate social and medical services. • Chronic Pain	Treatment of opioid dependence. (Note that buprenorphine single product buccal film; Belbuca; the transdermal patch and injections are indicated for use in pain management).	Maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low to moderate doses (≤8 mg/day) of a transmucosal buprenorphine-containing product for 3 months or longer with no need for supplemental dosing or adjustments	Opioid dependence: For the blockade of the effects of exogenously administered opioids (for the prevention of relapse to opioid dependence, following opioid detoxification) Alcohol dependence: Treatment of alcohol dependence (in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol)	Alcohol dependence and for the blockade of the effects of exogenously administered opioids

Table 1. Comparison of Maintenance Treatment Options for OUD[11,42,46-55]

	Methadone	***Buprenorphine Pill or film***	***Buprenorphine Implant***	***Extended Release Naltrexone***	***Oral Naltrexone***
Age	Adults (Manufacturers state that safety, efficacy, and pharmacokinetics not established in pediatric patients <18 years of age) Caution in elderly	Zubsolv, Bunavail: ≥16 years Buprenorphine sublingual tablets: safety and efficacy have not been established in pediatric patients. Caution in elderly or debilitated patients	Adults: the safety and efficacy have not been established in patients <16 years and studies did not include patients >65 years old	The safety, efficacy, and pharmacokinetics have not been established in the pediatric, elderly, or perinatal populations.	
Administration/ Convenience	• Daily dosing (with OTP oversight, which is good for compliance and minimizes diversion, however, may be difficult for patient to consistently attend) • Flexible dosing: recent evidence Cochrane review[56] & other review[57] noted greater treatment retention and lower cost associated with methadone vs buprenorphine when using flexible dosing	• Daily dosing, but can be given every 2 to 3 days as tolerated and can be filled at a local pharmacy (vs visiting a clinic daily) • Advantage: dosing flexibility • Films dissolve more quickly than tablets => advantage when monitored dose ingestion is indicated;[54,58] potentially enhanced patient satisfaction[59]	• 4 implants are inserted every 6 months; must be done by a certified healthcare provider. • Potential surgical complications (during insertion or removal): risk of implant migration, protrusion, expulsion, and nerve damage resulting from the procedure • Advantage: verifiable dosing	• Every 4 weeks/once a month administration • IM gluteal injection by healthcare provider (alternating buttocks) • Advantage: verifiable dosing	• Daily or every other day dosing • Has had historically low rates of compliance and retention
Setting	• Limited to specially licensed OTP prescribing and dispensing: (advantage: high structure of delivery setting), until the patient receives take-home doses. • Only licensed physicians who are DEA registered and who work at an OTP can order methadone for dispensing at the certified OTP or hospital. • Nicholls et al.[52] mention long waiting lists for entry into methadone maintenance treatment.	• Office-based or OTP setting; any pharmacy can fill the prescription • Increased accessibility to treatment and avoiding the stigma and other negative feelings associated with going to methadone clinic; requires an X-DEA number/waiver to prescribe in and office-based setting or the physician needs to be DEA registered and work at an OTP	• Office-based or OTP setting: providers must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE REMS program • Closed Distribution – only to healthcare providers certified in the Probuphine REMS Program can purchase the medication	• Any medical setting, requires injection by healthcare provider; can be prescribed by any licensed healthcare with prescribing authority (no special training required); • Can be purchased at a retail pharmacy (usually through the specialty division)	• Any medical setting • Providers do not have to have special certifications; prescriptions can be obtained at a retail pharmacy

Table 1. Comparison of Maintenance Treatment Options for OUD[11,42,46-55]

	Methadone	*Buprenorphine Pill or film*	*Buprenorphine Implant*	*Extended Release Naltrexone*	*Oral Naltrexone*
Adherence	Supervised and if compliant with treatment for 2 years, could receive a 30-day take-home dose.	May be lost or forgotten (if prescribed outside of an OTP)	Can't be lost or forgotten vs. daily; long-acting which should improve adherence	Can't be lost or forgotten vs. daily; long-acting which should improve adherence/facilitate compliance	
Abuse Potential or other limitations	Usually administered in OTP unless compliant for 2 years, could receive take-home supply which could be stolen misused or abused.	Could be stolen/misused/abused	Unlikely to be stolen/misused/abused. Contains a significant amount of drug that could lead to accidental exposure or intentional misuse or abuse if implant comes out of skin	Abuse unlikely; has not been associated with diversion or physical dependence Lower serum concentration toward the end of the dosing cycle compared to the beginning of the cycle may have overdose implications upon patient relapse	Abuse unlikely; has not been associated with diversion or physical dependence
Common Adverse Effects/ Safety Concerns	Sedation (especially early in treatment), constipation, QT prolongation Higher overdose incidence and mortality (1 of every 3 opioid-related deaths is associated with methadone ingestion). [48,60]	Lower extremity swelling, urinary hesitancy, constipation Appears to have a better safety profile (pending direct comparison studies) with regard to overdose vs methadone[52] or with respect to QT prolongation potential.[61]	Implant-site pain, itching, and redness, headache, depression, constipation, nausea, vomiting, back pain, toothache, and oropharyngeal pain	Injection site reactions, nausea/vomiting, malaise, hepatic enzyme abnormalities, toothache, insomnia, dizziness, appetite suppression, headache	Insomnia, anxiety, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache, loss of appetite, dizziness, rash

Table 1. Comparison of Maintenance Treatment Options for OUD[11,42,46-55]

	Methadone	*Buprenorphine Pill or film*	*Buprenorphine Implant*	*Extended Release Naltrexone*	*Oral Naltrexone*
Warnings / Precautions	• Overdosing • Drug-drug interactions involving CYP-enzymes • Respiratory insufficiency or suppression especially with concurrent BZPs/alcohol/CNS depressants • Hypersensitivity • Cardiac conduction abnormalities • Physical dependence; withdrawal upon abrupt discontinuation • Liver insufficiency • Neonatal withdrawal syndrome possible with perinatal use	• Respiratory insufficiency or suppression especially with concurrent BZPs/alcohol/CNS depressants • Hypersensitivity • Physical dependence; withdrawal upon abrupt discontinuation • Liver insufficiency • Drug-drug interactions involving CYP-enzymes • Anti-retrovirals: Some potential interactions, but appear to be fewer interactions vs methadone possibly due to different route of absorption (sublingual or buccal); less competitive.[54,62] • Neonatal withdrawal syndrome possible with perinatal use	• Potential serious complications from insertion and removal. Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion. Incomplete insertions or infections may lead to protrusion or expulsion. • See also pill/film applicable precautions	• Precipitated withdrawal if given before opioid free washout period; may be severe enough to require hospitalization (opioid-free period of 7-10 days is recommended; • Abstinence from opioids can be difficult for patients to achieve) • Vulnerability to opioid overdose • Injection site reactions/hypersensitivity • Hepatotoxicity • Depression and Suicidality: monitor patients • Pain management challenges	
Switching Therapy[9]	⇨ Methadone to buprenorphine: Better tolerated when on <30-40 mg of methadone; mono-buprenorphine product is recommended ⇨ Methadone to naltrexone: Must be completely withdrawn from opioids and be opioid free for at least 7 days (may take 14 days).	⇨ Buprenorphine to methadone: No delay needed ⇨ Buprenorphine to naltrexone: because of the long BUP half-life, it may take 7-14 days after last dose of buprenorphine to be opioid-free	⇨ Converting back to sublingual tablet**:** On day of implant removal, resume buprenorphine treatment at previous sublingual dose[63]	⇨ Naltrexone to buprenorphine: Wait 30 days for ER naltrexone (one day for oral naltrexone) ⇨ Naltrexone to methadone: Wait 30 days for ER naltrexone (one day for oral naltrexone). Use low initial dose of methadone.	

* Refer to individual package inserts for complete prescribing information on these agents

Abbreviation key: AE, adverse effects; BUP, buprenorphine; BZPs, benzodiazepines; CNS, central nervous system; CYP, cytochrome P450; HCV, hepatitis C virus; MOA, mechanism of action; NTX, naltrexone; OTP, opioid therapy program; OUD, opioid use disorder; RCT, randomized controlled trial; XR-NTX, extended release naltrexone

Table 2. Comparison of Buprenorphine Plasma Concentration Parameters[64,65]

	Sublocade		**Probuphine**	**Subutex**	
Mean	100 mg	300mg	80mg/implant	12 mg	24mg
C avg,ss (ng/mL)	3.2	6.5	0.5 to 1	1.7	2.9
Cmax,ss	4.9	10.1		5.4	8.3

Abbreviation: ss, steady state

Appendix B

Table 1. Randomized Controlled Trial Study Design

Study	Study Design
Phase 3, Randomized, Double-blind, Controlled Trial of RBP-6000 (NCT02357901)	Included patients seeking MAT, diagnosed per DSM-5 for moderate or severe OUD, and with history over the previous 3 months; with BMI of ≥ 18.0 to ≤ 35.0 kg/m^2 Excluded patients with a condition, other than OUD, requiring chronic opioid treatment; patients with substance use disorder regarding any substances other than opioids, cocaine, cannabis, tobacco, or alcohol; patients with a positive UDS at screening for cocaine or cannabis AND who meets DSM-5 criteria for either moderate or severe cocaine or cannabis use disorder, respectively; patients meeting DSM-5 criteria for moderate or severe alcohol use disorder; or patients that had MAT in the 90 days prior to providing written informed consent Run-in, open-label phase: Participants were inducted onto Suboxone film, then a 4 to 11-day dose-adjustment period to achieve stabilization from 8 to 24 mg of BUP. Upon randomization into blinded treatment arms, Suboxone was tapered from 6 mg to 2 mg from Days 1-5 and then discontinued. *Study Arms* **A**: BUP 300 mg SC every 4 weeks X 6 doses + IDC **B**: BUP 300 mg SC every 4 weeks for 2 doses+ IDC, followed by BUP 100 mg SC every 4 weeks for 4 doses + IDC **C**: volume-matched placebo to regimen A + IDC X 6 months **D**: volume-matched placebo to regimen B + IDC X 6 month Monitoring included weekly scheduled urine testing beginning at week 5

Abbreviation key: BMI, body mass index; BUP, buprenorphine; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; HR, hazard ratio; IDC, individual dug and behavior counselling; MAT, medication-assisted treatment for OUD; OUD, opioid use disorder; UDS, urine drug screen

Appendix C: Related ICD-10 Diagnosis Codes

MASTER ICD	
ICD	**Diagnosis**
3040	OPIOID TYPE DEPENDENCE
30400	OPIOID DEPENDENCE-UNSPEC
30401	OPIOID DEPENDENCE-CONTIN
30402	OPIOID DEPENDENCE-EPISOD
30403	OPIOID DEPENDENCE-REMISS

MASTER ICD	
ICD	**Diagnosis**
F1120	OPIOID DEPENDENCE, UNCOMPLICATED
F1121	OPIOID DEPENDENCE, IN REMISSION
F1123	OPIOID DEPENDENCE WITH WITHDRAWAL

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