



**Indian Health Service**  
**National Pharmacy and Therapeutics Committee**  
**Formulary Brief: Long-Acting Buprenorphine for OUD**  
**-July 2020-**



**Background:**

American Indians and Alaskan Natives (AI/AN) have higher rates of opioid overdose deaths than the general population and the second highest of any racial/ethnic group. In August 2018, the NPTC completed a comprehensive review of Opioid Use Disorder (OUD) and added buprenorphine/naloxone, buprenorphine (limited to management of OUD in pregnancy) and extended-release naltrexone to the National Core Formulary (NCF). In July 2020, the NPTC reviewed new long-acting formulations of buprenorphine for OUD and **no changes were made to the NCF.**

**Discussion:**

There are currently three FDA approved extended-release (ER) medications for the treatment of OUD and one currently seeking FDA approval. The first approved product was the naltrexone ER injection, Vivitrol<sup>®</sup>, reviewed in the [August 2018 NPTC Formulary Brief](#). The 2020 review focused on the two approved long-acting buprenorphine formulations for the treatment of OUD, Probuphine<sup>®</sup> and Sublocade<sup>®</sup>, as well as CAM2038, which is seeking FDA approval. These three ER medications contain the active ingredient buprenorphine, a partial mu agonist with weak kappa antagonist activity. Adverse drug reactions (ADRs) are similar to transmucosal buprenorphine and include headache, nausea, constipation, and vomiting. The ER buprenorphine formulations also produce noticeable injection site reactions. Substantial evidence supports buprenorphine as a Medication Assisted Treatment for OUD.

**Probuphine<sup>®</sup>** was FDA approved in 2016 and is a six-month implantable buprenorphine administered subdermally for the management of OUD.<sup>1</sup> The implant contains 320mg of buprenorphine (80mg per rod), equivalent to an 8 mg daily transmucosal buprenorphine dose. The implant contains 4 rods and is inserted into the inside of the upper arm. Patients aged  $\geq 16$  years must be stabilized on maintenance doses  $\leq 8$  mg/day of a transmucosal buprenorphine-containing product for 3 months or longer. The implants require office-based surgical insertion and must be removed after six months. A second set of rods can be placed in the other arm for another 6 months. After this second insertion, patients must transition back to a transmucosal buprenorphine-containing product. Product-specific ADRs (in addition to the general ADRs listed above) include depression, toothache, and oropharyngeal pain.<sup>1,6</sup>

**Sublocade<sup>®</sup>** received FDA approval in 2017 and is a once-monthly, prefilled syringe of buprenorphine administered subcutaneously in the abdominal area for management of OUD.<sup>2</sup> It is dosed as 300mg for the first two months, then 100mg monthly thereafter, however it can be given as 300mg monthly as indicated for withdrawal and cravings. This is intended as a maintenance treatment for moderate to severe OUD in patients initiated on 8 to 24mg of a transmucosal buprenorphine-containing product for a minimum of 7 days. Sublocade<sup>®</sup> carries a boxed warning as it can cause a life-threatening pulmonary embolus if given intravenously. ADRs reported (in addition to general ADRs listed above) include fatigue and elevated liver function enzymes.<sup>2,6</sup>

**CAM2038 (Brixadi<sup>®</sup>)** is currently under regulatory review with an expected approval date in December 2020.<sup>3</sup> CAM2038 is a buprenorphine injection that can be administered IM weekly (8mg, 16mg, 24mg, 32mg) or monthly (64mg, 96mg, 128mg) and is reportedly seeking indications for both initiation and maintenance treatment for OUD.<sup>3,6</sup> Additional ADRs include nasopharyngitis and urinary tract infections.<sup>8</sup> CAM2038 will be available in prefilled syringes which do not require refrigeration.<sup>6</sup>

**REM requirements:**

The [Probuphine REMS](#) program was developed in conjunction with the FDA to mitigate the risk of complications of migration, protrusion, expulsion, and nerve damage associated with insertion and removal of implants, as well as risks of accidental overdose, misuse, and abuse.<sup>4</sup> Healthcare providers performing insertions or removals of buprenorphine implants are required to enroll in the REMS program as well as complete live training and demonstrate competency on the procedure. Healthcare providers who do not have interest in performing these surgical procedures can become certified as prescribers only and must attend the training session and complete a knowledge test. Currently, Probuphine<sup>®</sup> is only available through specialty pharmacy programs.

The [Sublocade REMS](#) program is intended to ensure that it is only given by certified healthcare providers and never dispensed directly to the patient. Moreover, the REMS program ensures the appropriate training to avoid IV administration, which can form an occlusion or cause local tissue damage and result in thromboembolic events including PE.<sup>5</sup> Healthcare providers and pharmacies that dispense Sublocade<sup>®</sup> must be enrolled in the REMS program. Once enrolled, Sublocade<sup>®</sup> can be ordered through a specialty pharmacy program or for IHS pharmacies through McKesson<sup>®</sup> once verified.

### Findings:

The Institute for Clinical and Economic Review (ICER) 2018 reviewed ER opioid agonists and antagonists, focusing on the efficacy, safety and effectiveness of ER and transmucosal formulations.<sup>7</sup> Probuphine<sup>®</sup> and CAM2038 were studied in comparison to transmucosal buprenorphine/naloxone, while Sublocade<sup>®</sup> was only studied in comparison to placebo. ICER results demonstrated that discontinuation rates appeared similar with CAM2038, Probuphine<sup>®</sup>, and Vivitrol<sup>®</sup> vs. sublingual buprenorphine/naloxone. Common reasons for discontinuation included lack of efficacy, adverse events, withdrawing consent, being unable to complete induction, loss to follow-up, and withdrawal symptoms. Opioid craving scores on CAM2038 and Probuphine<sup>®</sup> were not significantly different from buprenorphine/naloxone. Sublocade<sup>®</sup> decreased opioid craving versus placebo. No significant differences were shown for CAM2038 or Probuphine<sup>®</sup> in comparison with buprenorphine/naloxone on opiate withdrawal scales and only the higher dose arm of Sublocade<sup>®</sup> showed any significant difference from placebo.

**Probuphine<sup>®</sup>** was also compared to buprenorphine/naloxone in a 24-week, Phase 3 double-blind, double dummy RCT.<sup>10</sup> This trial enrolled 177 participants (mean age 39 years; male: 59%) with heroin as the primary opioid in 21% and prescription drugs as primary opioid in 74%. Participants were clinically stable and receiving buprenorphine tablets for 24 weeks before the trial. The primary outcome was the difference in proportion of responders, defined as those with at least 4-6 months without evidence of illicit opioid use. The study demonstrated non-inferiority for buprenorphine implants and sublingual buprenorphine; 96.4% vs 87.6%, (97.5% CI: 0.009 to  $\infty$ ;  $p < 0.001$ ). At 6 months, rates of abstinence were 85.7% for buprenorphine implants and 71.9% for sublingual buprenorphine (HR 13.8; 95% CI: 0.02 to 0.26;  $p = 0.03$ ), NNT of 7.3. Additionally, time to first illicit opioid use was significantly longer for buprenorphine implants (HR 0.49, 95% CI: 0.25 to 0.97;  $p = 0.04$ ). No significant differences were found for opioid craving and withdrawal. Similar rates of discontinuation occurred between active arms, along with similar proportions of serious adverse events.

**Sublocade<sup>®</sup>** was compared to placebo in a 24-week, Phase 3 double-blind, placebo-controlled trial.<sup>8</sup> This trial enrolled 504 participants (66.7% male) randomized to one of three arms after an open-label, run-in induction phase with SL buprenorphine/naloxone and dose adjusted to 8 to 24 mg. Those randomized to the 100 mg dose group received an initial monthly dose of Sublocade<sup>®</sup> 300mg for two months before receiving a monthly 100 mg dose for four months, while the 300 mg group received a monthly dose of 300 mg for the six months. Participants also received individual counseling at least once a week. The primary outcome (percentage of urine samples combined with self-reports negative for illicit opioid use from weeks 5 to 24) for each group was 41.3% (300mg/300mg) and 42.7% (300mg/100mg) compared to placebo (5%);  $p < 0.001$  for both buprenorphine regimens.

**CAM2038** was compared to buprenorphine/naloxone in a 24-week Phase 3, double-blind, double-dummy, active-controlled RCT.<sup>9</sup> This trial enrolled 428 adults (61.4% male). Participants were given weekly doses of SL buprenorphine/naloxone + SC placebo or SL placebo + SC buprenorphine for the first 12 weeks. For the second 12 weeks, participants received dummy doses of either SL daily or monthly injections. CAM2038 was found to be non-inferior to buprenorphine. The proportion of opioid-negative urine samples was 28.4% and 35.1% respectively, for SL buprenorphine/naloxone and CAM2038, a 6.7% difference ( $p < 0.001$ ) but was not different in abstinence, opioid craving, and opioid withdrawal. Similarly, discontinuation rates were high but did not differ between arms, and safety profiles were comparable.

### Conclusions:

Buprenorphine formulations continue to have an established role in OUD treatment. Long-acting buprenorphine formulations have limited comparative data to SL buprenorphine and show non-inferiority. There are currently no head-to-head trials comparing long-acting buprenorphine products to each other or to ER naltrexone. The ER buprenorphine formulations offer patients and prescribers options to accommodate for patient needs. If approved, CAM2038 will offer expanded dosing options and weekly or monthly dosing regimens. There is no established data in women who are pregnant or breast-feeding and

should be avoided as dose adjustments are not feasible with Sublocade® and Probuphine®. Extended-release buprenorphine will certainly have a role to play in select populations and expands the available formulations and options for the treatment of OUD.

---

*If you have any questions regarding this document, please contact the NPTC at [IHSNPTC1@ihs.gov](mailto:IHSNPTC1@ihs.gov). For more information about the NPTC, please visit the [NPTC website](#).*

#### **References:**

1. Probuphine (buprenorphine) [[prescribing information](#)]. Princeton, NJ: Braeburn Pharmaceuticals Inc.
2. Sublocade (buprenorphine extended release) [[prescribing information](#)]. North Chesterfield, VA: Indivior Inc
3. Buprenorphine: Drug Information. Lexicomp. [https://www.uptodate.com/contents/buprenorphine-drug-information?search=buprenorphine&source=panel\\_search\\_result&selectedTitle=1~148&usage\\_type=panel&kp\\_tab=drug\\_general&display\\_rank=1#F143033](https://www.uptodate.com/contents/buprenorphine-drug-information?search=buprenorphine&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#F143033)
4. Probuphine REMS <http://www.probuphinerems.com/patients>
5. Sublocade REMS <https://www.sublocade.com/hcp/buprenorphine>
6. Parida S, Carroll KM, et al. [Buprenorphine treatment for opioid use disorder: recent progress](#). *Expert Rev Clin Pharmacol*. 2019; 12(8):791-803.
7. Institute for Clinical and Economic Review. [Extended release opioid agonists and antagonists medications for addiction treatment \(MAT\) for opioid use disorder: effectiveness and value](#). Published October 25, 2018.
8. Haight BR, Learned SM, Laffont CM, et al. [Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a randomized placebo-controlled, phase 3 trial](#). *Lancet*. 2019; 393(10173):778-790.
9. Lowfall MR, Walsh SL, Nunes EV, et al. [Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder a randomized clinical trial](#). *JAMA Intern Med*. 2018; 178(6):764-773.
10. Rosenthal R, Lofwall M, Kim S, et al. [Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine: a randomized clinical trial](#). *JAMA* 2016; 316:282-290.