BUPRENORPHINE (PROBUPHINE® & SUBLOCADE™)

Policy Number: PHARMACY 291.7 T2 **Effective Date**: December 1, 2018

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Related Policies
None

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CONDITIONS OF COVERAGE

Applicable Lines of Business/ Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General Benefits Package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes[1]
Precertification with Medical Director Review Required	Yes[1]
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Office[2]
Special Considerations	[1]Precertification with review by a Medical Director or their designee through Oxford's Medical Management is required. [2]**Participating Providers in the Office Setting**: Precertification is required for services performed in the

Special Considerations *(continued)*	office of a participating provider. **Non-Participating/ Out-of-Network Providers in the Office Setting:** Precertification is not required, but is encouraged for out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member-specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to: Acquired Rare Disease Drug Therapy Exception Process policy.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

This policy provides information about the use of buprenorphine formulations administered by either the subcutaneous (SC) or by subdermal implant. This policy refers to the following buprenorphine products:

- Probuphine®
- Sublocade™

Probuphine (buprenorphine) subdermal implant is proven and/or medically necessary for[1]:

The maintenance treatment of opioid dependence in patients who meet ALL of the following criteria:

- Patient has achieved and sustained prolonged clinical stability on transmucosal buprenorphine; **and**
- Patient is currently maintained on a dose of 8mg per day or less of oral, sublingual or transmucosal buprenorphine product equivalent [e.g., Subutex 8 mg or less, Suboxone (or generic equivalent) 8 mg/2 mg or less, Bunavail 4.2 mg/0.7 mg or less, or Zubsolv 5.7 mg/1.4 mg or less]; **and**
- Patient has been on a stable oral, sublingual or transmucosal buprenorphine dose for six months or longer without any need for supplemental dosing or adjustments; **and**
- Prescriber meets DATA 2000 requirements and has been assigned a unique identification number specific to the prescription of medication assisted therapy (DEA-X); **and**
- Prescriber and/or the healthcare provider performing insertion has successfully completed a live training program specific to Probuphine insertion; **and**
- Submission of medical records (e.g., chart notes, laboratory values) documenting **one** of the following:
  - **Initial therapy** with Probuphine when meeting **all** of the following:[1,3]
    - Patient has a viable site for implant on the upper arm (inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus in the sulcus between the biceps and triceps muscle).
    - Patient will not be receiving supplemental oral, sublingual or transmucosal buprenorphine.
    - Patient has not had an opioid-positive urine drug screen within the previous ninety days prior to insertion.*

    or
  - **Continuation therapy** with Probuphine when meeting **all** of the following:[1,3]
    - Patient has only had one Probuphine implant and has a viable, unused site in the contralateral arm.
    - Patient has not, nor will receive supplemental oral, sublingual, or transmucosal buprenorphine.
    - Probuphine is not being inserted into a previously used arm or insertion site.

- Probuphine is only to be used in a maximum of 2 insertions (once in each arm).
- Patient shows no evidence of tampering, extraction, or attempted removal of the previous Probuphine implant.
- Patient has not had an opioid-positive urine drug screen since starting Probuphine therapy.*****

Buprenorphine extended-release injection (e.g., Sublocade) is proven and/or medically necessary for:

The treatment of moderate to severe opioid use disorder in patients who meet ALL of the following criteria:

- For **initial therapy**, **all** of the following:
  - Patient is currently maintained on a 8mg to 24mg per day dose of oral, sublingual, or transmucosal buprenorphine product equivalent for at least 7 days prior to initiation of extended-release buprenorphine injection; **and**
  - Patient has not, nor will receive supplemental, oral, sublingual, or transmucosal buprenorphine; **and**
  - Prescriber meets DATA 2000 requirements and has been assigned a unique identification number specific to the prescription of medication assisted therapy (DEA-X); **and**
  - Sublocade dosing for is in accordance with the U. S. Food and Drug Administration approved labeling: 300mg subcutaneously monthly for the first 2 months, followed by a maintenance dose of 100 mg or 300mg monthly; **and**
  - Initial authorization will be for no more than 6 months.

  or
- For **continuation therapy**, **all** of the following::
  - Physician documentation that the patient has experienced positive clinical response to buprenorphine extended-release therapy; **and**
  - Patient has not, nor will receive supplemental, oral, sublingual, or transmucosal buprenorphine; **and**
  - Prescriber meets DATA 2000 requirements and has been assigned a unique identification number specific to the prescription of medication assisted therapy (DEA-X); **and**
  - Sublocade dosing is in accordance with the U. S. Food and Drug Administration approved labeling: Maintenance dose of 100 mg or 300mg monthly; **and**
  - Continuation authorization will be for no more than 12 months.

***Note**: Patients screening positive for opioid use outside of an opioid dependence treatment regimen is evidence that the patient has not achieved or is no longer in sustained, prolonged, clinical stability with their treatment program. Use of Probuphine is not indicated in this population. Patients should use sublingual or transmucosal buprenorphine until the patient can achieve sustained, prolonged, clinical stability on a low-to-moderate dose (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent).

Buprenorphine extended-release injection is unproven and not medically necessary for pain management.[1,3,6]

Probuphine is unproven and not medically necessary for:[1,3]

- Patients who have not achieved and sustained prolonged clinical stability and tolerance to opioids for at least six months.
- Patients who are maintained on sublingual or transmucosal buprenorphine at doses greater than 8 mg per day.
- Patients who are recently tapered to a lower dose of sublingual or transmucosal buprenorphine for the sole purpose of transitioning to Probuphine.
- Patients who are new entrants to opioid dependence treatment.
- Patients who have already had one insertion in each arm.
- Patient who do not have viable sites for insertion in the upper arm.
- Patients who have an opioid-positive urine drug screen within the previous ninety days.
- Patient is currently being treated for chronic pain requiring opioids.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Probuphine is indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a sublingual or transmucosal buprenorphine containing product (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent).[1] Each Probuphine implant is an ethylene vinyl acetate (EVA) implant, 26 mm in length and 2.5 mm in diameter, containing 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride).

Probuphine should be used as part of a complete treatment program to include counseling and psychosocial support.

Probuphine is not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability, while being maintained on buprenorphine 8 mg per day or less of a Subutex or Suboxone sublingual tablet or generic equivalent.

Probuphine is available only through a restricted REMS program, called the "Probuphine REMS Program", because of the risk of complications of migration, protrusion and expulsion, and nerve damage associated with the insertion and removal of Probuphine.

Notable requirements of the "Probuphine REMS Program" include the following:

- Healthcare providers who **Prescribe** Probuphine must be certified with the program by enrolling and completing live training
- Healthcare providers who **Insert** Probuphine:
  - Must meet the prerequisite requirements
  - Must be certified with the program by enrolling and completing live training, including demonstrating competency in Probuphine procedures
- Patients must be monitored to ensure that Probuphine is removed by a healthcare provider certified to insert/remove Probuphine implants
- Probuphine will only be distributed to certified prescribers through a restricted distribution program.

There is no experience with inserting additional implants into other sites in the arm to recommend an approach to a second insertion into a previously-used arm. Neither re-insertion into previously-used administration sites, nor into sites other than the upper arm, have been studied. It is important to avoid previously-implanted sites because the effect of scarring and fibrosis in previously-used insertion sites on either the effectiveness of Probuphine or the safety of insertion have not been evaluated. After one insertion in each arm, additional cycles of treatment should only be considered if the potential benefits of continuing Probuphine outweigh the potential risks of additional insertion and removal procedures, taking into account the experience of the health care provider with Probuphine procedures and related procedures, and the clinical need of the patient for ongoing treatment with subdermal medication. In most cases, patients should be transitioned back to a transmucosal buprenorphine-containing product for continued treatment.

Sublocade is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days. Sublocade should be used as part of a complete treatment plan that includes counseling and psychosocial support.[6]

Sublocade is available only through a restricted REMS program, called the "Sublocade REMS Program", because of the risk of serious harm or death that could result from intravenous self-administration. Healthcare settings and pharmacies that order and dispense Sublocade must be certified in this program and comply with the REMS requirements.

Substance Abuse and Mental Health Services Administration (SAMHSA)[4]

Verification of DATA-Certified Physicians

Effective July 25, 2005, physicians must include their DATA 2000 waiver ID number on prescriptions for opioid addiction treatment medications. The practitioner's DEA registration number and the unique identification number (DATA 2000 waiver ID number or "X" number) must be on the prescription 21 CFR 1306.05(a). The identification number is not in lieu of the DEA registration number, it is an addition. If the prescription is telephoned to the pharmacy, the pharmacist must have both of these numbers on the prescription record so the physician can provide the numbers or the pharmacist may have them on file.

The SAMHSA Buprenorphine Physician Locator web site lists the physicians in each State who have DATA 2000 waivers. A physician listed on the site can be considered to have a valid DATA 2000 waiver. **Note, however, that the site does not list every physician with a valid waiver, only those who have agreed to be listed on the site.** Physicians with valid waivers may choose not to be listed on the site.

A person desiring to verify that a physician who is not listed on the site has a valid DATA 2000 waiver can contact SAMHSA by phone at 1-866-BUP-CSAT (1-866-287-2728) or by e-mail at infobuprenorphine@samhsa.hhs.gov The verifying person should convey their DEA registration number with these requests.

BACKGROUND

Probuphine (buprenorphine) implant is a sterile, single, off-white, soft, flexible rod-shaped drug product. It is 26 mm in length and 2.5 mm in diameter. Each implant contains 74.2 mg buprenorphine (equivalent to 80 mg buprenorphine

hydrochloride) and ethylene vinyl acetate (EVA). Probuphine is designed to be implanted subdermally by a trained medical professional and to provide sustained delivery of buprenorphine for up to six months.

Four Probuphine rods deliver circulating drug blood levels comparable to the average plasma concentrations observed following daily doses of ≤ 8 mg buprenorphine or buprenorphine/naloxone sublingual or transmucosal products.

Sublocade (buprenorphine-extended release) is a sterile solution for subcutaneous injection only. It is designed to deliver buprenorphine at a controlled rate over a one month period.

Buprenorphine hydrochloride is an opioid partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor, thus it exhibits a ceiling to its effects. The danger of overdose, abuse liability, and toxicity may be less than with full opioid agonists.[2]

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

CPT Code	Description
11981	Insertion, non-biodegradable drug delivery implant
11982	Removal, non-biodegradable drug delivery implant

CPT® is a registered trademark of the American Medical Association

HCPCS Code	Description
G0516	Insertion of non-biodegradable drug delivery implants, 4 or more (services for subdermal rod implant)
G0517	Removal of non-biodegradable drug delivery implants, 4 or more (services for subdermal implants)
G0518	Removal with reinsertion, non-biodegradable drug delivery implants, 4 or more (services for subdermal implants)
J0570	Buprenorphine implant, 74.2 mg
Q9991	Injection, buprenorphine extended-release (Sublocade), less than or equal to 100 mg
Q9992	Injection, buprenorphine extended-release (Sublocade), greater than 100 mg

ICD-10 Diagnosis Code	Description
F11.20	Opioid dependence, uncomplicated
F11.21	Opioid dependence, in remission

CLINICAL EVIDENCE

The efficacy of Sublocade for the treatment of opioid use disorder was evaluated in a Phase 3, 24-week, randomized, double-blind, placebo-controlled, multicenter trial in treatment-seeking patients with moderate or severe opioid use disorder.[6] Patients (n=504 patients) were randomized 4:4:1:1 to one of following dosing regimens: 6 once-monthly 300 mg doses (n=203), 2 once-monthly 300 mg doses followed by 4 once-monthly 100 mg doses (n=201), or 6 once-monthly SC injections of placebo (n=100). All doses were administered by a physician or suitably qualified designee and were separated by 28 ± 2 days. In addition to study medication, all subjects received manual-guided psychosocial support at least once a week (Individual Drug Counseling = IDC). Prior to the first dose, treatment was initiated with buprenorphine/naloxone sublingual film; doses were adjusted from 8/2mg to 24/6 mg per day over a period of 7-14 days. Patients were randomized to Sublocade injection or placebo after cravings and withdrawal symptoms were clinically controlled. After randomization, supplemental dosing with buprenorphine/naloxone film was not permitted during the study. Efficacy was evaluated over Weeks 5 through 24 based on weekly urine drug screens combined with self-reported use of illicit opioid use. A "grace period" was applied for Weeks 1 through 4 to allow patients to stabilize in treatment. During this period, opioid use, if it occurred, was not considered in the analysis. Missing urine drug screen samples and/or self-reports during Weeks 5-24 were counted as positive for illicit opioids. Based on the cumulative distribution function (CDF) of the percentage of urine samples negative for illicit opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24, regardless of dose, Sublocade was superior to the placebo group with statistical significance. The proportion of patients achieving

treatment success (defined as patients with ≥80% opioid-free weeks) was statistically significantly higher in both groups receiving Sublocade compared to the placebo group (28.4% [300 mg/100 mg], 29.1% [300 mg/300mg], 2% [placebo].

The efficacy of Probuphine was demonstrated in an outpatient, randomized, active controlled, double-blind, double-dummy, multi-center, study in adults who met DSM-IV-TR criteria for opioid dependence as their primary diagnosis, and were considered clinically stable, on a sublingual buprenorphine dose of no more than 8 mg per day, by their treating Healthcare Provider.[1,3] Patients included in the study were those prescribed daily sublingual buprenorphine for 6 months or more, were abstinent while taking 8mg/d or less of sublingual buprenorphine for 90 days or longer, and were determined to be clinically stable by their physician. Eligible participants also showed no evidence of opioid withdrawal or illicit opioid-positive urine samples for at least 90 days prior to study entry. Participants were to randomized to receive either sublingual buprenorphine plus 4 placebo implants or sublingual placebo plus four 80mg buprenorphine implants for a 24 week trial period. Of 177 participants (mean age, 39 years; 40.9%female), 90 were randomized to sublingual buprenorphine with placebo implants and 87 to buprenorphine implants with sublingual placebo. Exclusion criteria included, but weren't limited to lack of appropriate implant sites (recent scars, history of keloids); primary diagnosis of substance dependence other than opioids or nicotine; or pending legal action or other factors/conditions that could adversely affect participant safety and adequate adherence. Patients were seen monthly for six months and were also required to provide four randomly-scheduled urine samples for toxicology. Efficacy was evaluated through urine toxicology screening and patient self-report to detect opioid use, over the 6-month treatment period. Supplemental dosing with open-label sublingual buprenorphine/naloxone tablets was permitted as clinically indicated. Of the 177 participants, 165 of 177 (93.2%) completed the trial. Eighty-one of 84 (96.4%) receiving buprenorphine implants and 78 of 89 (87.6%) receiving sublingual buprenorphine were responders, an 8.8% difference (1-sided 97.5%CI, 0.009 to ∞; P < .001 for noninferiority). Over 6 months, 72 of 84 (85.7%) receiving buprenorphine implants and 64 of 89 (71.9%) receiving sublingual buprenorphine maintained opioid abstinence (hazard ratio, 13.8; 95%CI, 0.018-0.258; P = .03). Non–implant-related and implant-related adverse events occurred in 48.3% and 23% of the buprenorphine implant group and in 52.8% and 13.5% of participants in the sublingual buprenorphine group, respectively. The authors concluded that the use of buprenorphine implants compared with continued sublingual buprenorphine did not result in an inferior likelihood of remaining a responder. However, the study population had an exceptionally high response rate in the control group, and further studies are needed in broader populations to assess the efficacy in other settings.

REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy, Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [*2018D0056G*]

1. Probuphine [package insert]. Princeton, NJ: Braeburn Pharmaceuticals, Inc., May 2016.
2. Gold Standard, Inc. Probuphine®. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed July 20, 2017.
3. Rosenthal RN, Lofwall MR, Kim S, Chen M, Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial. JAMA. 2016 Jul 19;316(3):282-90.
4. Buprenorphine Treatment Physician Locator. (n.d.). Retrieved July 20, 2017, from http://www.samhsa.gov/medication-assisted-treatment/physician-program-data/treatment-physician-locator.
5. Probuphine Insertion & Removal Instruction Booklet. Princeton, NJ: Braeburn Pharmaceuticals, Inc., May 2016. Available at: http://probuphinerems.com/wp-content/uploads/2016/04/ifu.pdf.
6. Sublocade [package insert]. Burlington, MA: Indivior Inc., March 2018.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
12/01/2018	• Updated conditions of coverage/special considerations; modified notation to clarify: ○ For **participating providers in the office setting**: Precertification is required for services performed in the office of a participating provider ○ For **non-participating/out-of-network providers in the office setting**: Precertification is not required, but is encouraged for out-of-network services performed in the office; if precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered

Date	Action/Description

	• Revised coverage rationale:
	  ○ Updated coverage criteria for the use of buprenorphine extended-release injection (e.g., Sublocade) for the treatment of moderate to severe opioid use disorder:
	  ▪ Replaced criterion requiring "Sublocade dosing is in accordance with the U. S. Food and Drug Administration (FDA) approved labeling: 300mg subcutaneously monthly for the first 2 months, followed by a maintenance dose of 100 mg *monthly; dosing may be increased to* or 300mg monthly" with "Sublocade dosing is in accordance with the FDA approved labeling: 300mg subcutaneously monthly for the first 2 months, followed by a maintenance dose of 100 mg or 300mg monthly"
	  ▪ Replaced criterion for continuation therapy requiring "patient has experienced *treatment success* to buprenorphine extended-release therapy" with "*physician documentation that the* patient has experienced *a positive clinical response* to buprenorphine extended-release therapy"
	  ○ Modified language to clarify the services are unproven ***and*** not medically necessary (as described)
	• Updated supporting information to reflect the most current references
	• Archived previous policy version PHARMACY 291.6 T2