**PROBUPHINE® (BUPRENORPHINE)**

**Policy Number**: 2017D0057B  
**Effective Date**: February 1, 2017

### Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTRUCTIONS FOR USE</td>
<td>1</td>
</tr>
<tr>
<td>BENEFIT CONSIDERATIONS</td>
<td>1</td>
</tr>
<tr>
<td>U.S. FOOD AND DRUG ADMINISTRATION</td>
<td>2</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>APPLICABLE CODES</td>
<td>4</td>
</tr>
<tr>
<td>CLINICAL EVIDENCE</td>
<td>4</td>
</tr>
<tr>
<td>CENTERS FOR MEDICARE AND MEDICAID SERVICES</td>
<td>4</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>5</td>
</tr>
<tr>
<td>POLICY HISTORY/REVISION INFORMATION</td>
<td>5</td>
</tr>
</tbody>
</table>

### INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. 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 Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug 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 Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

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.

### 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 enrollee-specific benefit 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. See the Policy and Procedure addressing the treatment of serious rare diseases.

### 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

Probuphine (buprenorphine) subdermal implant is proven and medically necessary for:

1. The maintenance treatment of opioid dependence in patients who meet all of the following criteria:
   a. Patient has achieved and sustained prolonged clinical stability on transmucosal buprenorphine.
   AND
   b. Patient is currently maintained on a dose of 8mg per day or less of 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
   c. Patient has been on a stable sublingual or transmucosal buprenorphine dose for six months or longer without any need for supplemental dosing or adjustments.
   AND
   d. Prescriber meets DATA 2000 requirements and has been assigned a unique identification number specific to the prescription of medication assisted therapy (DEA-X).
   AND
   e. Prescriber and/or the healthcare provider performing insertion has successfully completed a live training program specific to Probuphine insertion.
   AND
   f. Submission of medical records (e.g., chart notes, laboratory values) documenting One of the following:
      (1) Initial therapy with Probuphine when meeting all of the following:¹,³
         (a) 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).
         (b) Patient is participating in behavioral therapy/peer support program.
         (c) Patient will not be receiving supplemental sublingual or transmucosal buprenorphine.
         (d) Patient has not had an opioid-positive urine drug screen within the previous ninety days prior to insertion.*
      OR
      (2) Continuation therapy with Probuphine when meeting all of the following:¹,³
         (a) Patient has only had one Probuphine implant and has a viable, unused site in the contralateral arm.
         (b) Patient is participating in behavioral therapy/peer support program.
         (c) Probuphine is not being inserted into a previously used arm or insertion site.
         (d) Probuphine is only to be used in a maximum of 2 insertions (once in each arm).
         (e) Patient shows no evidence of tampering, extraction, or attempted removal of the previous Probuphine implant.
         (f) Patient has not had an opioid-positive urine drug screen since starting Probuphine therapy.*

*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).

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

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

U.S. FOOD AND DRUG ADMINISTRATION

Probuphine is indicated for the maintenance treatment of opioid dependence in patients who have achieved and
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.

**Substance Abuse and Mental Health Services Administration (SAMHSA)**

*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](http://www.buprenorphine.samhsa.gov) 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 [info@buprenorphine.samhsa.gov](mailto:info@buprenorphine.samhsa.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.
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.  

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.

**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 and Coverage Determination Guidelines may apply.

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<td>11981</td>
<td>Insertion, non-biodegradable drug delivery implant</td>
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<tr>
<td>11982</td>
<td>Removal, non-biodegradable drug delivery implant</td>
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<tr>
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<td>F11.20</td>
<td>Opioid dependence, uncomplicated</td>
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<tr>
<td>F11.21</td>
<td>Opioid dependence, in remission</td>
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**CLINICAL EVIDENCE**

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.  

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 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 = .30). 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.

**CENTERS FOR MEDICARE AND MEDICAID SERVICES**

Medicare does not have a National Coverage Determination (NCD) for PROBUPHINE® (buprenorphine). Local Coverage Determinations (LCDs) do not exist at this time.

Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at [http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf](http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf).
REFERENCES


POLICY HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tbody>
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<td>2/1/2017</td>
<td>Off cycle review. Added continuing therapy criterion requiring behaviorally therapy/support program participation. Approved by the National Pharmacy &amp; Therapeutics Committee on 12/21/2016. Policy 2017D0057A archived.</td>
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<tr>
<td>1/1/2017</td>
<td>New policy 2017D0057A. Approved by National Pharmacy &amp; Therapeutics Committee on 8/19/2016.</td>
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