Clinical Policy: Buprenorphine HCL (Probuphine Implant)

Reference Number: NH.PHAR.289
Effective Date: 11/2016
Last Review Date: 06/2017 Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for buprenorphine (Probuphine® Implant).

Policy/Criteria
It is the policy of health plans affiliated with Centene Corporation® that Probuphine is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Opioid Dependence (must meet all):

1. Diagnosis of opioid dependence;
2. Member has met all the following for at least the last 3 months:
   a. Demonstrated clinical stability (i.e., no supplemental buprenorphine doses or dose adjustments) on a product equivalent to a Suboxone/Subutex sublingual tablet buprenorphine dose of ≤ 8 mg per day *(see Appendix B for product equivalencies - sublingual or buccal formulations only);*
   b. No evidence or reports of the following:
      i. Illicit opioid use (confirmed with at least one random urine drug screen within the last 3 months);
      ii. Significant withdrawal symptoms;
      iii. Significant desire/need to use illicit opioids;
      iv. Hospitalizations, emergency room visits or crisis interventions for addiction or mental health issues;
      v. Nonadherence to clinic visits or drug abuse counseling as recommended;
3. Member will participate in a drug abuse counseling program while on therapy;
4. Probuphine prescription is for four implants to be placed for every 6 months (see Appendix C for dosing and administration information);
5. Member does not have moderate to severe hepatic impairment;
6. Member has no known hypersensitivity to buprenorphine or any other ingredients in Probuphine including ethylene vinyl acetate (EVA) (e.g., bronchospasm, angioneurotic edema, or anaphylactic shock with symptoms of rash, hives or pruritus).

Approval duration: up to 12 months (two sets of four implants)
The four implants are inserted subdermally in the inner side of the upper arm.

B. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

II. Continued Approval

A. Opioid Dependence (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member has met all the following during the last approval period:
   a. If a supplemental buprenorphine-containing product was prescribed it was prescribed (needed) only intermittently rather than on an ongoing basis;
   b. If member received other opioids (see Appendix D for examples of opioids) during the last approval period, documentation is submitted confirming use was due to a diagnosis of pain;
   c. No evidence or reports of the following:
      i. Illicit opioid use (confirmed with at least two random urine drug screens since last approval);
      ii. Significant withdrawal symptoms;
      iii. Significant desire/need to use illicit opioids;
      iv. Hospitalizations, emergency room visits or crisis interventions for addiction or mental health issues;
      v. Nonadherence to clinic visits;
      vi. Nonadherence to drug abuse counseling (participation confirmed with documentation);
3. Probuphine prescription is for four implants to be placed every 6 months;
4. Member has not previously received four sets of implants (one set is defined as four implants per arm);
5. Member has none of the following reasons to discontinue:
   a. Known hypersensitivity to buprenorphine or any other ingredients in Probuphine, including EVA (e.g., bronchospasm, angioneurotic edema, or anaphylactic shock with symptoms of rash, hives or pruritus);
   b. Moderate to severe hepatic impairment.

Approval duration: up to 12 months (a maximum of four sets of four implants)
The four implants are inserted subdermally in the inner side of the OPPOSITE upper arm.

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy**.**

Background
Description/Mechanism of Action:
Probuphine (buprenorphine hydrochloride [HCL]) is designed to be implanted subdermally by a trained medical professional and to provide sustained delivery of buprenorphine for up to 6 months (each 6-month dose represents four implants). Buprenorphine is an opioid partial agonist at the mu opioid receptor and an antagonist at the kappa-opioid receptor and is regulated as a Schedule III controlled substance/narcotic (C-III) under the United States Controlled Substances Act.

Because of the risks associated with implant insertion and removal, Probuphine is available only through a restricted program called the PROBUPHINE REMS Program (see package insert for more details, including exception at Appendix E). Additionally, under the Drug Addiction Treatment Act (DATA) codified at 21 United States Code (U.S.C.) 823(g), use of Probupine in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, have notified the Secretary of Health and Human Services of their intent to prescribe or dispense this product for the treatment of opioid dependence, and have been assigned a unique identification number that must be included on every prescription.

Formulations:
Each Probuphine implant kit contains the following:

- One individually packaged sterile disposable applicator (used to insert all four implants)
- Four individually packaged sterile implants
  - Each implant is 26 mm in length and 2.5 mm in diameter and contains 74.2 mg of buprenorphine (equivalent to 80 mg buprenorphine HCL) and ethylene vinyl acetate (EVA).
  - Four Probuphine implants (320 mg buprenorphine HCL) deliver circulating drug blood levels comparable to the average plasma concentrations observed following daily doses of ≤ 8 mg of Subutex/Suboxone sublingual tablet equivalencies.

FDA Approved Indications:
Probuphine (buprenorphine) is a partial opioid agonist/subdermal implant indicated for:

- Maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet equivalent or generic equivalent).

  - *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 equivalent or generic equivalent.*

Appendices
Appendix A: Abbreviation Key
DATA: Drug Addiction Treatment Act
HCL: Hydrochloric acid
U.S.C.: United States Code
EVA: Ethylene vinyl acetate
NOWS: Neonatal opioid withdrawal syndrome

Appendix B: Brand/Generic Transmucosal Formulations Equivalent to Subutex or Suboxone Sublingual Tablets Containing ≤ 8 mg of Buprenorphine

Drug	Transmucosal* Formulation	Brand/Generic†	Brand/Generic Strength	Subutex/Suboxone‡ Sublingual Tablet Strength
			Buprenorphine/Naloxone§ Equivalency	
Buprenorphine HCL	Tablet, sublingual	Generic	2 mg 8 mg	2 mg (Subutex) 8 mg (Subutex)
Buprenorphine HCL/naloxone HCL	Tablet, sublingual	Generic	2 mg/0.5 mg 8 mg/2 mg	2 mg/0.5 mg (Suboxone) 8 mg/2 mg (Suboxone)
		Zubsolv	1.4 mg/0.36 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg	2 mg/0.5mg (Suboxone) 4 mg/1 mg (Suboxone) 8 mg/2 mg (Suboxone)
	Film, buccal	Bunavail	2.1 mg/0.3 mg 4.2 mg/0.7 mg	4 mg/1 mg (Suboxone) 8 mg/2 mg (Suboxone)
	Film, sublingual or buccal	Suboxone	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg	2 mg/0.5 mg (Suboxone) 4 mg/1 mg (Suboxone) 8 mg/2 mg (Suboxone)

**Transmucosal formulations include buprenorphine and buprenorphine/naloxone sublingual tablets and buccal/sublingual films.*
†For a more comprehensive listing of brand/generic sublingual/buccal transmucosal formulations see the U.S. Food & Drug Administration Orange Book: Approved drug products with therapeutic equivalence evaluations at http://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm.
‡Subutex (buprenorphine) and Suboxone (bupronorphine/naloxone) sublingual tablets, while used as buprenorphine equivalency references, are no longer available in the U.S.
§Naloxone (an opioid antagonist) is minimally absorbed in sublingual/buccal transmucosal formulations and rather is added to discourage diversion or misuse.

Appendix C: Dosing and Administration Information

- Probuphine subdermal implants are intended to be in place for 6 months and then removed by the end of the sixth month or earlier if needed.
- If continued treatment is desired new implants are inserted subdermally at the time of removal of the first implant. The new implants are placed in an area of the inner side of either upper arm that has not been previously used.
- If new implants are not inserted on the same day as the removal of implants, patients are maintained on their previous dosage of transmucosal buprenorphine (i.e., the dose from which they were transferred to Probuphine treatment) prior to additional Probuphine treatment.
- After one insertion in each arm, most patients should be transitioned back to a transmucosal buprenorphine-containing product for continued treatment.
- Patients who elect to discontinue Probuphine treatment without continuing on other buprenorphine treatment should be monitored for withdrawal.
    - Withdrawal signs and symptoms can include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

- Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy and is a risk if members using Probuphine are pregnant (see package insert for more information).

Appendix D: Opioids and Opioid Antagonists

- Opioids
  - Naturally occurring opioids (opiates): Morphine, codeine
  - Semi-synthetic opioids: Heroin (a derivative of morphine not used therapeutically in the U.S.), hydrocodone, oxycodone
  - Synthetic opioids: Buprenorphine, fentanyl, methadone, tramadol
- Opioid antagonists
  - Naloxone
  - Naltrexone

Appendix E: Overdosage Information

- Clinical presentation:
  - The manifestations of acute buprenorphine overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.
- Treatment of overdose:
  - In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.
  - The opioid antagonist naloxone is a specific antidote to respiratory depression resulting from opioid overdose. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.
  - Clinicians should consider the potential role and contribution of buprenorphine, other CNS depressant drugs, and other opioids in a patient's clinical presentation, in determining whether the implants should be removed. In an emergency situation, the removal procedure can be performed by a surgeon who is not certified in the REMS.

Reviews, Revisions, and Approvals	Date	Approval Date
New policy created.	11/16	11/16
Adjusted duration of approval to up to 12 months as well as criteria	06/17	

References

1. Probuphine [implant] Prescribing Information. Princeton, NJ: Braeburn Pharmaceuticals, Inc.; May 2016. Available at http://probuphine.com/wp-content/uploads/2016/02/final-approved-pi.pdf. Accessed November 2, 2016.
2. Suboxone [sublingual/buccal film] Prescribing Information. Richmond, VA: Indivior, Inc.; June 2016. Available at http://www.indivior.com/products/. Accessed November 2, 2016.

3. Zubsolv [sublingual tablet] Prescribing Information. Morristown, NJ: Orexo US, Inc.; October 2016. Available at https://www.zubsolv.com/wp-content/uploads/2015/01/ZubsolvFullPrescribingInformation.pdf. Accessed November 3, 2016.
4. Bunavail [buccal film] Prescribing information. Raleigh, NC: BioDelivery Sciences International, Inc.; April 2015. Available at https://bunavail.com/hcp/pdf/BUNAVAIL_Full_Prescribing_Information.pdf?pdf=BUNAVAIL-Full-Prescribing-Information. Accessed November 3, 2016.
5. Buprenorphine: Drug information. In: UpToDate (Lexicomp), Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed November 3, 2016.
6. Buprenorphine and naloxone: Drug information. In: UpToDate (Lexicomp), Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed November 3, 2016.
7. Buprenorphine. Orange Book: Approved drug products with therapeutic equivalence evaluations. U.S. Food & Drug Administration. Available at http://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm. Accessed November 3, 2016.
8. 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.* July 19, 2016; 316(3): 282-90. Open access link: http://jama.jamanetwork.com/article.aspx?articleid=2533504. Accessed December 2, 2016.
9. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Substance Abuse and Mental Health Services Administration. 2004; report no. (SMA) 04-3939. Available at https://www.ncbi.nl m.nih.gov/books/NBK64245/. Accessed November 4, 2016.
10. Strain E. Opioid use disorder: Epidemiology, pharmacology, clinical manifestations, course, screening, assessment, and diagnosis. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed November 4, 2016.
11. Strain E. Pharmacotherapy for opioid use disorder. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed November 4, 2016.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits

are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.