

Clinical Policy: Buprenorphine HCL (Probuphine Implant)

Reference Number: PA.CP.PHAR.289

Effective Date: 01/2018

Last Review Date: 11/2016

[Revision Log](#)

Description

The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness[®] clinical policy for buprenorphine (Probuphine[®] Implant).

Policy/Criteria

It is the policy of Pennsylvania Health and Wellness[®] 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 up to 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 6 months (one set of four implants)

The four implants are inserted subdermally in the inner side of the upper arm.

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

II. Continued Approval

A. Opioid Dependence (must meet all):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;;
2. Member has met all the following during the last approval period:
 - a. 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;
 - b. 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 for up to 6 months;
4. Member has not previously received two 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 6 months (a second [and last] set 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 Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.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 muopioid 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

CLINICAL POLICY

Buprenorphine HCL



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 Probupine 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 Probupine 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:

Probupine (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).
 - *Probupine should be used as part of a complete treatment program to include counseling and psychosocial support.*
 - *Probupine 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
			<i>Buprenorphine/Naloxone§ Equivalency</i>	
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/0.5 mg (Suboxone) 4 mg/1 mg (Suboxone) 8 mg/2 mg (Suboxone)
		Bunavail	2.1 mg/0.3 mg 4.2 mg/0.7 mg	4 mg/1 mg (Suboxone) 8 mg/2 mg (Suboxone)
	Film, 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 (buprenorphine/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

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.nlm.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.