Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Buprenorphine Implant for Treatment of Opioid Dependence

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for the buprenorphine implant when it is determined to be medically necessary because the following criteria have been met.

When Policy Topic is covered

Buprenorphine subdermal implants may be considered medically necessary when all four of the following criteria have been met:

1. The individual has been diagnosed with opioid dependence; **and**
2. The individual has been treated with a stable transmucosal buprenorphine dose (≤8 mg/d of a sublingual Subutex or Suboxone tablet or its transmucosal buprenorphine product equivalent) for 3 months or more without any need for supplemental dosing or adjustments; **and**
3. The individual is currently on a maintenance dose* of 8 mg per day or less of a sublingual Subutex or Suboxone tablet or its transmucosal buprenorphine product equivalent to achieve sustained prolonged clinical stability on transmucosal buprenorphine; **and**
4. Buprenorphine implants are used as part of a comprehensive substance use disorder treatment program that includes counseling and psychosocial support.

* Food and Drug Administration indications specify that maintenance doses should not be tapered to a lower dose for the sole purpose of transitioning to buprenorphine implants (Braeburn Pharmaceuticals, 2017).

Inserting up to 4 buprenorphine implants once in each arm at an interval of 6 months may be considered medically necessary.

When Policy Topic is not covered

Buprenorphine implants are considered investigational for all other indications, including but not limited to:

1. When the medically necessary criteria above have not been met.
2. For new entrants to treatment.
3. For individuals who have not achieved and sustained prolonged clinical stability while being maintained on buprenorphine 8 mg or less per day of a Subutex or Suboxone sublingual tablet or generic equivalent.
4. For individuals not enrolled in a comprehensive substance use disorder treatment program.
5. Treatment for longer than 12 months.

Individuals can be transitioned back to transmucosal buprenorphine-containing medications for continued treatment after 12 months as needed. Retreatment with buprenorphine implant after a prior 12-month treatment period is considered investigational and not medically necessary under all circumstances.

The prescribing information also provides guidance on acceptable doses of transmucosal buprenorphine that demonstrating stable maintenance dosing (Braeburn Pharmaceuticals, 2017):

- Buprenorphine (Subutex) sublingual tablet (generic equivalent) 8 mg or less per day.
- Buprenorphine and naloxone (Suboxone) sublingual tablet (generic equivalent) 8 mg/2 mg or less per day.
- Buprenorphine and naloxone (Bunavail™) buccal film 4.2 mg/0.7 mg or less per day.
- Buprenorphine and naloxone (Zubsolv®) sublingual tablets 5.7 mg/1.4 mg or less per day.

Additionally, the prescribing information includes the following factors in determining clinical stability and suitability for Probuphine treatment (Braeburn Pharmaceuticals, 2017):

- Period free from illicit opioid drug use.
- Stability of living environment.
- Participation in a structured activity/job.
- Consistent participation in recommended behavioral therapy/peer support program.
- Consistent compliance with clinic visit requirements.
- Minimal to no desire or need to use illicit opioids.
- Period without episodes of hospitalizations (addiction or mental health issues), emergency room visits, or crisis interventions.
- Social support system.

Considerations

Buprenorphine implant claims are managed via ClaimsXten.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Hayes Medical Technology Directory, Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers

Description of Procedure or Service

Buprenorphine is a partial μ-opioid agonist used to treat patients with an opioid addiction. Administered transmucosally, buprenorphine can be used with or without naloxone, which is an opioid antagonist. Though effective, a clinical strategy of using transmucosal buprenorphine is prone to nonadherence, diversion, abuse, and accidental misuse. To lower these risks and improve adherence, Braeburn Pharmaceuticals has developed buprenorphine (Probuphine), an implant to provide sustained delivery of buprenorphine for up to 6 months via 4 subdermally inserted rods. Probuphine is intended as a maintenance treatment for a selected subgroup of opioid-dependent patients who are clinically stable on a low dose of transmucosal buprenorphine (≤8 mg/d). These implants are inappropriate for new treatment recipients and those who do not have sustained and prolonged clinical stability while being maintained on a generic equivalent of buprenorphine.

For individuals who are addicted to opioids but stable on low-to-moderate doses of transmucosal buprenorphine who receive buprenorphine implants, the evidence includes a randomized controlled trial. Relevant outcomes are change in disease status, morbid events, health status measures, medication use, and treatment-related morbidity. In the pivotal trial, the proportion of patients who reported for no more than 2 out of 6 months any evidence of illicit opioid use was similar between the buprenorphine implant arm (63%) and the sublingual buprenorphine arm (64%). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Rationale

Buprenorphine is among the main options in a medication-assisted treatment strategy for opioid dependence. Transmucosal buprenorphine products have a potential for diversion to an illicit drug

market and have resulted in accidental poisonings of small children.1 To minimize the misuse, Braeburn Pharmaceuticals developed Probuphine, an implantable buprenorphine that would be difficult to divert or abuse, and therefore would less likely be accidentally ingested by children. Further, it would maximize adherence passively for 6 or 12 months as it is an implant. The initial new drug application (NDA) submitted by Braeburn in October 31, 2012, sought approval of buprenorphine implants for initial treatment of patients with opioid dependence after just a few days of titration on a transmucosal formulation. The Food and Drug Administration issued a complete response letter for this NDA, stating that, although the two 6-month trials met the prespecified end points, the dose provided by the implant "was too low to provide effective treatment for patients new to buprenorphine treatment." 2 However, data from a subset of patients revealed that 4 buprenorphine implants yielded buprenorphine concentrations similar to those observed with sublingual buprenorphine (anywhere from 4 to 8 mg based on average exposure [eg, mean area under the receiver operating characteristic curve values] or concentration). Thus, a subset of patients stabilized on sublingual buprenorphine 8 mg or less could benefit from buprenorphine implants, which is the current target population for which these implants are approved

REGULATORY STATUS On May 26, 2016, buprenorphine implant (Probuphine®; Braeburn Pharmaceuticals, Princeton, NJ) was approved by the U.S. Food and Drug Administration through the NDA process for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of an agent containing transmucosal buprenorphine (ie, doses of ≤8 mg/d of Subutex® or Suboxone® [Indivior Inc, Richmond, VA] sublingual tablet or generic equivalent).

Pivotal Trial Overview Evidence of the clinical efficacy of buprenorphine implants for the current Food and Drug Administration (FDA)–approved indication comes from a randomized, double-blind, double-dummy, active-controlled, multicenter trial. The trial evaluated the safety and efficacy of four buprenorphine 80-mg implants in adult outpatients with opioid dependence who were receiving sublingual buprenorphine 8 mg or less and considered clinically stable by their treating health care provider. 2,3 The trial included individuals ages 18 to 65 years who met DSM-IV criteria for opioid dependence as a primary diagnosis. These individuals were screened (for up to 3 weeks) and then randomized to receive sublingual buprenorphine tablets (≤8 mg/d) plus 4 placebo implants or four buprenorphine 80-mg implants plus daily sublingual placebo tablets for 24 weeks, and they were then tracked for 2-week follow-up phase. Supplemental dosing with sublingual buprenorphine plus naloxone tablets was permitted in both treatment arms. Clinical stability was confirmed using the following criteria at randomization: (1) individuals must have been on sublingual buprenorphine treatment for at least 6 months (≥24 weeks); (2) individuals must have been on a stable sublingual buprenorphine dose of 8 mg per day or less for at least the last 90 days; and (3) individuals must not have tested positive on a urine toxicology test for illicit opioids in the last 90 days. Trial-eligible individuals were also required to be free from significant withdrawal symptoms (Clinical Opiate Withdrawal Scale score ≤5). Individuals were excluded from the trial if they: • required opioid treatment for a current chronic pain condition or had a nonopioid dependence; • had elevated hepatic enzyme, bilirubin, or creatinine levels; • had low platelets or were on coagulopathy or anticoagulant treatment; • had recent scarring or tattoos on upper arms, or keloid scarring; • used CYP3A4 inhibitors; • had an AIDS diagnosis; or • had other medical or psychiatric conditions (as determined at the investigators' discretion). The primary efficacy end point was the proportion of responders defined as any patient with no more than 2 out of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use was defined as either a positive opioid urine toxicology test result or self-reported illicit opioid use. Trial participants provided 10 urine tests each—6 during the monthly visits and 4 randomly scheduled.
The trial was designed to test the noninferiority of the buprenorphine implant compared with sublingual buprenorphine. According to investigators' assumptions, the buprenorphine implant would be noninferior to sublingual buprenorphine if the lower bound of the 95% confidence interval (CI) for the implant's responder rate treatment difference was less than the noninferiority margin of 20%.4,5 However, because these assumptions used in calculating the noninferiority margin differed from the observed data, FDA, in its final approval of buprenorphine implants, did not permit a claim of

noninferiority even though the lower bound of treatment difference was less than 20%. The FDA-approved label only provides descriptive analysis of the data.6

Pivotal Trial Results A total of 176 individuals were randomized; of these, 173 received study medication and were included in the modified intention-to-treat (ITT) analysis by the sponsor. There were no significant differences in the baseline characteristics between the 2 study arms. Overall, patients' mean age was 39 years, 59% were male, 95% were white, and the primary opioid of abuse was as a prescription pain reliever. The median time since first reported use of opioids was 11.3 years, time since first diagnosis was 6.2 years, and median duration of buprenorphine treatment was 2.8 years. The study completion rate was 93% (81/87) in the buprenorphine implant arm and 94% (84/90) in the sublingual buprenorphine arm.2,3 In the FDA-approved label, response rates in buprenorphine implant arm and sublingual buprenorphine arm were 63% (55/87) and 64% (57/89), respectively, yielding a treatment difference of -1% (95% CI, -15% to 13%).6 The 2016 published report provided a much higher response rate.7 In the modified ITT analysis, the percentages of responders in the respective arms were 96% (81/87) and 88% (78/89%), yielding a treatment difference of 9% (95% CI, 1% to 17%; p=0.03 for superiority of the implanted over sublingual buprenorphine). In the ITT analysis, the respective response rates were 93% (81/87) and 88% (78/89), yielding a treatment difference of 6% (95% CI, -3% to 14%; p=0.22 for superiority of implanted over sublingual buprenorphine). Differences between the FDA data2,3 and a 2016 published article7 relate to the respective approaches to analyzing missing data. In the article, missing data were imputed by taking the mean of the intrasubject positive rate for that treatment arm and then applying a 20% penalty for the buprenorphine implant arm to take a conservative approach. FDA considered missing samples as evidence of opioid use and therefore classified those results as positive. Further, the use of supplemental sublingual buprenorphine in the buprenorphine implant arm was interpreted to indicate that the dose of buprenorphine provided by implant was inadequate for that patient (to maintain stability) and such patients were also classified as positive even if they showed no evidence of opioid use. None of the patients who received rescue doses in the trial required rescue doses in the 6 months before trial entry. Two additional studies have been published. 8,9 They included patients who were new entrants (after just a few days of titration on a transmucosal formulation) to buprenorphine treatment. Both studies were submitted as part of the new drug application in 2013. Although both met their prespecified end points, FDA determined that the dose provided by the implants was too low to provide effective treatment for patients new to buprenorphine treatment; therefore, the new drug application was rejected. These studies are not discussed further. The prescribing information explicitly states: "Probuphine should not be used for individuals who are new entrants to buprenorphine treatment or who have not 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 a Subutex or Suboxone sublingual tablet or generic equivalent, because the dose appears to be too low to be effective in these populations."

Harms The important potential harms of implant use are the risk of implant migration, protrusion, expulsion, and nerve damage resulting from the procedure. The safety of buprenorphine implants was evaluated in 349 opioid-dependent individuals across 3 double-blind trials (n=309) and 2 open-label extension studies (n=40). In these studies, 258 individuals were exposed to buprenorphine implants for at least 24 weeks, and 82 individuals were exposed for 48 weeks. Adverse events commonly associated with buprenorphine implants (>10% of individuals) were implant-site pain, pruritus, and erythema, as well as non-implant-site related events (≥5%) such as headache, depression, constipation, nausea, vomiting, back pain, toothache, and oropharyngeal pain.6 SUMMARY OF EVIDENCE For individuals who are addicted to opioids but stable on low-to-moderate doses of transmucosal buprenorphine who receive buprenorphine implants, the evidence includes a randomized controlled trial. Relevant outcomes are change in disease status, morbid events, health status measures, medication use, and treatment-related morbidity. In the pivotal trial, the proportion of patients who reported for no more than 2 out of 6 months any evidence of illicit opioid use was similar between the buprenorphine implant arm (63%) and the sublingual buprenorphine arm (64%). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. SUPPLEMENTAL INFORMATION PRACTICE GUIDELINES AND POSITION STATEMENTS American College of Physicians The American College of Physicians (ACP) published a

position paper on health and public policy to facilitate effective prevention and treatment of substance use disorders involving illicit and prescription drugs.10 ACP made recommendations specific to buprenorphine. As one of a number of strategies to address the epidemic of prescription drug misuse, ACP recommended “improved training in the treatment of substance use disorders, including buprenorphine-based treatment” as well as to “lift barriers that impede access to medication to treat opioid use disorder (methadone, buprenorphine, and naltrexone) and to medications for overdose prevention (naloxone)”.

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Billing Coding/Physician Documentation Information

HCPCS	J0570	Buprenorphine implant, 74.2 mg
CPT	17999	Unlisted procedure, skin, mucous membrane and subcutaneous
	11981	Insertion, non-biodegradable drug delivery implant

ICD-10_CM	F11.10-F11.99	Opioid related disorders code range (the company lists only F11.10, F11.20 and F11.21 as their recommended codes)

Additional Policy Key Words

5.01.26

Policy Implementation/Update Information

09/2018	New Policy titled Buprenorphine Implant for Treatment of Opioid Dependence – managed via CHC edit only