Buprenorphine (Brixadi™ & Sublocade®)

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Instructions for Use

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Coverage Rationale

See Benefit Considerations

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

- Brixadi™
- Sublocade®

Buprenorphine extended-release injection (e.g., Brixadi, Sublocade) is proven and 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 being treated for opioid dependence; **and**
  - **One** of the following:
    - **Both** of the following:
      - Patient is not currently receiving maintenance buprenorphine treatment; **and**
      - Patient has received a test dose of buprenorphine to establish that buprenorphine is tolerated without precipitated withdrawal;

      or
    - Patient is currently maintained on oral, sublingual, or transmucosal buprenorphine product;

    and
  - Patient has not, nor will receive supplemental, oral, sublingual, or transmucosal buprenorphine; **and**
  - Brixadi or Sublocade dosing is in accordance with the U. S. Food and Drug Administration approved labeling; **and**
  - Initial authorization will be for no more than 12 months.
- For **continuation of therapy**, **all** of the following:
  - Documentation of positive clinical response to buprenorphine extended-release therapy; **and**
  - Patient has not, nor will receive supplemental, oral, sublingual, or transmucosal buprenorphine; **and**
  - Brixadi or Sublocade dosing is in accordance with the U. S. Food and Drug Administration approved labeling; **and**
  - Continuation authorization will be for no more than 12 months.

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

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 Guidelines may apply.

HCPCS Code	Description
J0576	Injection, buprenorphine extended-release (Brixadi), 1 mg
Q9991	Injection, buprenorphine extended-release (Sublocade), less than or equal to 100 mg
Q9992	Injection, buprenorphine extended-release (Sublocade), greater than 100 mg

Diagnosis Code	Description
F11.20	Opioid dependence, uncomplicated
F11.21	Opioid dependence, in remission
F11.220	Opioid dependence with intoxication, uncomplicated
F11.221	Opioid dependence with intoxication delirium
F11.222	Opioid dependence with intoxication with perceptual disturbance
F11.229	Opioid dependence with intoxication, unspecified
F11.24	Opioid dependence with opioid-induced mood disorder
F11.250	Opioid dependence with opioid-induced psychotic disorder with delusions
F11.251	Opioid dependence with opioid-induced psychotic disorder with hallucinations
F11.259	Opioid dependence with opioid-induced psychotic disorder, unspecified
F11.28	Opioid dependence with other opioid-induced disorder (Incomplete code - additional digit required)
F11.281	Opioid dependence with opioid-induced sexual dysfunction
F11.282	Opioid dependence with opioid-induced sleep disorder
F11.288	Opioid dependence with other opioid-induced disorder
F11.29	Opioid dependence with unspecified opioid-induced disorder

Background

Brixadi (buprenorphine extended-release) injection is a sterile solution intended for subcutaneous injection only. Brixadi is designed to deliver buprenorphine at a controlled rate over either one week or one month.[10]

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]

Benefit Considerations

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 the Policy and Procedure addressing the treatment of serious rare diseases.

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.[6,7] 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 and safety of Brixadi for the treatment of opioid use disorder was evaluated in a Phase 3, 24-Week, randomized, double-blind, double-dummy, active controlled, multicenter study in patients who met the DSM-5 criteria for moderate or severe opioid use disorder and who were actively seeking but not currently receiving buprenorphine treatment.[10] Patients were randomized to receive either Brixadi injections with placebo sublingual tablets or sublingual buprenorphine/naloxone (SL BPN/NX) tablets with placebo injections. All patients received individual drug counseling for the duration of the study. On the first day of treatment patients received an open-label 4 mg test dose of sublingual buprenorphine. Patients who tolerated the test dose (two patients did not tolerate the test dose) were randomized and given a 16 mg injection of Brixadi (weekly) or matched placebo. During the next 6 days patients were allowed up to two further 8 mg injections as needed. Patients received an injection of 16, 24, or 32 mg on Day 8 matched to the dose they received in the previous seven days. Patients received injections weekly (every 7 days +/- 2-day window) for twelve weeks total and then transitioned to an equivalent dose of Brixadi (monthly) (every 28 days, +/- 7-day window) for the remaining twelve weeks. Dose adjustments were permitted for the duration of the study. Supplemental 8 mg Brixadi (weekly) injections were allowed during the second phase of the study and were also used in the active-controlled group. Overall, supplemental 8 mg injections were given to 14 patients (6.6%) in the Brixadi arm and 17 patients (7.9%) in the SL BPN/NX arm. For the first twelve weeks patients completed weekly visits. For the final twelve weeks patients were transitioned to monthly visits. Patients were also required to complete three additional randomly scheduled visits during the final twelve weeks. Efficacy was evaluated using urine drug screens combined with self-reported use of illicit opioid use. Missing urine drug screen samples and/or self-reports were counted as positive for illicit opioids. A total of 428 patients were randomized equally (215 patients in the SL BPN/NX group and 213 in the Brixadi group). Of the randomized patients, 69.0% (147/213) of the patients in Brixadi treatment group and 72.6% (156/215) of the patients in the SL BPN/NX treatment group completed the 24-week period. A patient was a responder if they met all of the following criteria:

- Negative opioid assessment (urinalysis and self-report) during week 12 (evaluated during week 13 visit).
- No more than one positive opioid assessment in the three illicit opioid use assessments performed during week 9 to 11 (evaluated during visits at weeks 10 to 12).
- Negative opioid assessment during the final month of the study.
- No more than one positive opioid assessment at the three scheduled monthly visits and three random site visits.

This responder definition was designed to identify patients who were successfully treated with both Brixadi (weekly) (administered in the first 12 weeks of treatment) and Brixadi (monthly) (administered in the second 12 weeks of treatment). Therefore, patients were required to have negative opioid assessments at the end of each treatment phase. Each phase also included an allowable grace period (an initial period of time when positive opioid assessments were not taken into account) and the definition also allowed for sporadic positive assessments. Brixadi met the primary endpoint of non-inferiority for responder rate vs. daily SL BPN/NX (16.9% vs. 14.0%; treatment difference of 2.9; 95% CI: -3.9, 9.8).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Brixadi is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. Brixadi should be used as part of a complete treatment plan that includes counseling and psychosocial support.

Brixadi is available only through a restricted program called the Brixadi REMS because of the risk of serious harm or death that could result from intravenous self-administration. The goal of the REMS is to mitigate serious harm or death that could result from intravenous self-administration by ensuring that healthcare settings and pharmacies are certified and only dispense Brixadi directly to a healthcare provider for administration by a healthcare provider. Healthcare Settings and Pharmacies that order and dispense Brixadi must be certified in the Brixadi REMS.

Sublocade is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a 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)[4,9]

Removal of DATA Waiver (X-Waiver) Requirement

Section 1262 of the Consolidated Appropriations Act, 2023 (also known as Omnibus bill), removes the federal requirement for practitioners to submit a Notice of Intent (have a waiver) to prescribe medications, like buprenorphine, for the treatment of opioid use disorder. All practitioners who have a current DEA registration that includes Schedule III authority may now prescribe buprenorphine for Opioid Use Disorder in their practice if permitted by applicable state law. All prescriptions for buprenorphine only require a standard DEA registration number. The previously used DATA-Waiver registration numbers are no longer needed for any prescription. There are no longer any limits or patient caps on the number of patients a prescriber may treat for opioid use disorder with buprenorphine. The Act does not impact existing state laws or regulations that may be applicable.

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Policy History/Revision Information

Date	Summary of Changes

01/01/2024	**Applicable Codes**
	• Updated list of applicable HCPCS codes to reflect annual edits:
	  ○ Replaced J3490 and J3590 with J0576
	  ○ Removed C9154
	Supporting Information
	• Archived previous policy version 2023D0057O

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies 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.