Extended-Release Buprenorphine Protocol

General info: Extended-release injectable buprenorphine (XR- or ER-bup) is a long-acting injectable form of buprenorphine, a partial opioid agonist, given subcutaneously every week to month. Several different formulations and strengths are available.

Dosage Forms and Strengths:

SUBLOCADE®: 100mg/0.5mL and 300mg/1.5mL injection in prefilled, single-dose syringes with 19 Gauge 5/8-inch needle.

BRIXADI® (weekly): 8mg/0.16mL, 16mg/0.32mL, 24mg/0.48mL, and 32mg/0.64mL in prefilled, single-dose syringes with 23 Gauge 1/2-inch needle.

BRIXADI® (monthly): 64mg/0.18mL, 96mg/0.27mL, and 128mg/0.36mL in prefilled, single-dose syringes with 23 Gauge 1/2-inch needle.

Dosing and Administration:

SUBLOCADE:

FDA Indications: Treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of transmucosal buprenorphine product, or who are already being treated with buprenorphine.

Initiation:
Patients already taking sublingual buprenorphine, 8-24mg daily:

- Injection #1:
  - Proceed directly to initiation with Sublocade 300mg SQ injection.
- Injection #2:
  - Schedule Sublocade 300mg SQ injection for 1 month after the initial injection. Injection #2 can be moved up to as early as 1 week after injection #1 depending on clinical response.

Patients NOT already taking sublingual buprenorphine:

- Injection #1:
  - Prior to injection #1, give an initial dose (e.g. 4mg) of sublingual buprenorphine and observe patient for one hour to confirm tolerability. If tolerated, a dose of Sublocade 300mg SQ injection can be administered.
- Injection #2:
  - Schedule Sublocade 300mg SQ injection for 1 month after the initial injection. Injection #2 can be moved up to as early as 1 week after injection #1 depending on clinical response.

Maintenance: Starting with injection #3, continue 100mg SQ monthly in the abdominal subcutaneous tissue. Some patients may require 300mg SQ maintenance dose. Rotate injection sites each month. Give

doses at least 26 days apart. Steady state is achieved 4-6 months after therapy initiation. Average buprenorphine serum levels are ~10% higher with SQ injection compared with SL tablets.

Injection Sites:
Administer in the subcutaneous tissue of the:

- Abdomen between the transpyloric and transtubercular planes
- Back of the upper arm
- Buttock
- Thigh

Missed doses: A patient who misses a dose should receive the next dose as soon as possible. Occasional delays in dosing of up to 2 weeks are not expected to have a clinically significant impact on treatment. If patients are later than 2 weeks for their injection, reinitiation using SL buprenorphine may be necessary.

BRIXADI:

FDA Indications: Treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of transmucosal buprenorphine product, or who are already being treated with buprenorphine.

Initiation:
Patients already taking sublingual buprenorphine:

- Switch directly to dosing Brixadi (weekly) or Brixadi (monthly) injections at the approximate equivalent maintenance dosing (see table below).

Daily dose of sublingual buprenorphine	BRIXADI (weekly)	BRIXADI (monthly)
≤ 6 mg	8 mg	--
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

Figure 1: Equivalent doses of daily sublingual buprenorphine and Brixadi. Source: prescribing info

Patients NOT already taking sublingual buprenorphine:
Weekly dosing:

- Injection #1:
  - Prior to injection #1, give an initial dose (e.g. 4mg) of sublingual buprenorphine and observe patient for one hour to confirm tolerability. If tolerated, a dose of Brixadi (weekly) 16mg SQ can be administered.
- Injection #2:
  - Within 3 days of injection #1, administer Brixadi (weekly) 8mg SQ dose to reach a target dose of Brixadi (weekly) 24mg.
- Injection #3 (optional):
  - At least 24 hours after injection #2, if clinically indicated, administer an additional 8 mg dose of BRIXADI (weekly), for a total weekly dose of 32 mg BRIXADI (weekly).

Maintenance:
Brixadi (weekly): Administer subsequent Brixadi (weekly) injections every 7 days, based on the total weekly dose that was established during Week One. Dose adjustments can be made weekly with the maximum dose being Brixadi (weekly) 32mg. Rotate injection sites each visit.

Brixadi (monthly): Administer subsequent Brixadi (monthly) SQ doses every 28 days. Dose adjustments can be made monthly, up to a maximum dose of Brixadi (monthly) 128mg. Dose adjustments should be made in 8mg increments, and can be given as additional Brixadi (weekly) 8mg injections. Rotate injection sites each visit.

Injection Sites:
Administer in the subcutaneous tissue of the:

- Abdomen
- Upper arm (in patients new to buprenorphine, this site should only be used after steady state or four consecutive doses; this site associated with 10% lower plasma levels than other sites).
- Buttock
- Thigh

Missed doses: A patient who misses a dose of Brixadi should be given the next dose as soon as possible. Brixadi (weekly) may be administered up to 2 days before or after the weekly time point. Brixadi (monthly) may be administered up to 1 week before or after the monthly time point.

Monitoring and Adverse Effects:

Common Adverse Effects: 5% or more: constipation, headache, nausea, vomiting, injection site pain (Sublocade), erythema (Brixadi), or pruritis, increased hepatic enzymes (Sublocade), fatigue, urinary tract infection (Brixadi).

Warnings and Precautions:

- Risk of serious harm or death with intravenous administration (boxed warning). Risk of serious injection site reactions, with increased risk with accidental intradermal or intramuscular administration.
- Risk of withdrawal in patients dependent on full opioid agonists (mitigated by administering a test dose or stabilizing on transmucosal buprenorphine prior to injection).
- Respiratory depression and overdose, especially with concomitant use of other CNS depressants. Provide naloxone and education on use to all patients taking buprenorphine products.
- Addiction, abuse and misuse. Monitor patients for diversion and progression of addictive behaviors.
- Neonatal opioid withdrawal syndrome (NOWS) is an expected outcome of prolonged opioid agonist use during pregnancy. Standard of care is to treat opioid use disorder in pregnancy with buprenorphine or methadone.

Drug Interactions:

- CYP3A4 Inhibitors and Inducers: Buprenorphine is a substrate of CYP3A4. Monitor patients starting or ending CYP3A4 inhibitors or inducers for signs and symptoms of increased or decreased serum levels of buprenorphine.
- Serotonergic Drugs: Opioid agonists may increase effects of serotonergic medications, raising the risk of serotonin syndrome. Monitor for serotoninergic toxicity, particularly during treatment initiation, and during dose adjustment of the serotonergic drug.

Contraindications:

- Allergy or hypersensitivity to buprenorphine.
- Moderate-severe hepatic impairment: not recommended.

Monitoring:

- Urine Drug Screen, including fentanyl and buprenorphine screen: every 1-2 visit during initiation phase, and less frequently when stable (every 1-6 months).
- LFTs semi-annually to annually.
- Urine buprenorphine/norbuprenorphine levels: NOT routinely monitored for Sublocade, as primary utility is to assess adherence. May consider in unusual cases where adherence is a concern.

Discontinuation: Extended-release buprenorphine should be continued as long as the patient is receiving benefit. If the medication is discontinued, patients may not experience withdrawal symptoms until several weeks later due to extended-release characteristics of medication.

Clinic Workflow

In addition to the usual workflow for long-acting injectable administration, there are additional requirements for extended-release buprenorphine formulations (Sublocade and Brixadi) since they are schedule III controlled medications.

Ordering from Pharmacy: At least 1 week before injection, prescription orders for Sublocade or Brixadi are electronically sent to a pharmacy registered with SUBLOCADE REMS or BRIXADI REMS. As of 2025, these include 1) San Mateo Medical Center outpatient pharmacy, and 2) Genoa Pharmacy, and 3) Safeway Pharmacy. Add a note requesting delivery to the regional clinic by date of injection. Prescribers are NOT required to register with REMS (unless keeping a bulk supply of Sublocade or Brixadi in stock at the clinic, which is not the case at BHRS clinics).

Delivery to Clinic: Sublocade or Brixadi is delivered to the clinic. The medication arrives as a pre-filled syringe. On arrival, two medical staff need to sign to receive the medication. See attached BHRS pharmacy form for receiving and storing controlled substances below.

Storage:

- Sublocade: Store in the locked refrigerator at 2°C to 8°C (35.6°F to 46.4°F) inside the med room. The med room can only be accessed by staff with badge access. Once outside the refrigerator, may be stored at room temperature, 15°C to 30°C (59°F to 86°F), for up to 12 weeks prior to administration. Discard if left at room temperature for longer than 12 weeks.
- Brixadi: Store in a locked cabinet at room temperature at 20°C to 25°C (68°F to 77° F) in the med room. Excursions permitted at 15°C to 30° C (59°F to 86°F)

Scheduling: Patients are scheduled for injections by the provider or nurse, in line with current workflow for other LAIs.

Staffing: Sublocade is typically administered by the clinic RNs, consistent with current workflow for other LAIs. MDs may also administer Sublocade depending on clinic practices.

Administration: Sublocade is generally administered with the patient lying supine on an exam table. See injection step-by-step checklist below for detailed steps for administration.

Monitoring: Post-injection monitoring is not generally needed, unless a patient not currently taking buprenorphine is given the Sublocade injection after receiving a single test dose. In this scenario,

monitor the patient in the healthcare setting for worsening signs of withdrawal or sedation. The patient should be stable or improving prior to leaving the healthcare setting. The prescribing MD and/or MOD will be available to triage any issues that arise after the appointment.

Naloxone: Provide naloxone to all patients on buprenorphine products, either by prescription or from the clinic med room. Provide education on how to administer naloxone. Document that naloxone was provided or that patient already has naloxone.

Disposal: Used syringes are disposed in the locked disposal bins used for all sharps. There is no additional requirement for disposal of used medication. Unused medication syringes should be disposed in accordance with BHRS policy, which requires 2 signatures (from RN, MD, or PharmD staff) witnessing storage of controlled medications in designated white containers marked for removal and incineration.

References:

1. Brixadi® [package insert]. Braeburn Inc., Plymouth Meeting, PA; Dec, 2023. Accessed June 3, 2025.
2. Sublocade® [package insert]. Indivior Inc., North Chesterfield, VA; Feb, 2025. Accessed June 3, 2025.
3. Protocol for Buprenorphine/Naloxone (Suboxone®) for Opioid Use Disorder in Outpatient Settings. BHRS Medical & Pharmacy Information, San Mateo County Health. Accessed June 3, 2025.
4. Buprenorphine: Drug Information. UptoDate® Lexidrug™ 2025. Accessed June 3, 2025.

SAMPLE COPY OF CONTROLLED SUBSTANCE RECORD

SAN MATEO COUNTY HEALTH
BEHAVIORAL HEALTH & RECOVERY SERVICES

Controlled Substances/Emergency Supply Record

Site: _____ **Date:** _____

Medication _____ **Strength** _____ **Lot #** _____

Received by _____ **Amount** _____ **Expiration Date** _____

Amount Used	Amount Remaining	Date	Client or Other Disposition	Signature(s) (two signatures for controlled substances)