Grayken Center for Addiction Training & Technical Assistance

Boston Medical Center

BUPRENORPHINE EXTENDED-RELEASE IMPLEMENTATION GUIDE

Table of Contents

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Acknowledgments

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Introduction

This document serves as a comprehensive guide for the implementation of buprenorphine extended-release injection (BUPE-ER) for the treatment of opioid use disorder (OUD) within healthcare settings. It aligns with the current rules and regulations of the Drug Enforcement Administration (DEA) and the Food and Drug Administration's (FDA) medication-specific Risk Evaluation and Mitigation Strategies (REMS) requirements. Sites must adhere to federal and state regulations governing medication procedures, including the logging, ordering, receiving, tracking, administering, and disposal of buprenorphine extended-release injection. Additionally, organization-specific policies often include administration procedures, documentation, and patient tracking.

This guide outlines key components for the successful implementation of buprenorphine extended-release injection. It covers relevant definitions, identifies regulatory bodies, and highlights educational and training resources and tools to ensure regulatory compliance while providing high-quality patient care.

Given the dynamic regulatory landscape and the potential for additional formulations of buprenorphine extended-release injection, sites should periodically review federal and state regulations to ensure practices, including proper medication disposal, adhere to the current recommendations and regulations.

At the time of the most recent revision of this document, there are two FDA-approved formulations of buprenorphine extended-release injection available for use:

- **SUBLOCADE®** (buprenorphine/DL-lactide-co-glycolide polymer/NMP) and
- **BRIXADI®**
    - **Weekly** (buprenorphine/anhydrous ethanol/soybean phosphatidylcholine/glycerol dioleate)
    - **Monthly** (buprenorphine/soybean phosphatidylcholine/glycerol dioleate/NMP) (FDA, 2023-a; FDA 2023-b)

This document's content applies to managing Schedule III medications for the treatment of OUD. Appendices or resources specific to a particular formulation are titled accordingly.

Helpful Terminology and Definitions

Buprenorphine is a Schedule III medication. Formulas approved under DATA 2000 for the treatment of moderate to severe OUD require handling and security in compliance with federal and state regulations, as well as organization and site-specific policies.

Buprenorphine extended-release injection (BUPE-ER) is an FDA-approved formulation of buprenorphine for the treatment of moderate to severe OUD. Due to the risk of overdose or serious health complications associated with misuse or improper use of buprenorphine extended-release injection, the DEA and FDA regulate the handling and administration of this medication (FDA 2023-a, 2023, FDA-2023-b). The healthcare team should always manage buprenorphine extended-release injections; patients should never handle this medication due to safety risks. Buprenorphine extended-release injection is exclusively available through FDA-mandated programs known as Risk Evaluation and Mitigation Strategies (REMS) Programs.

Buprenorphine prescribers must have an unencumbered license, a valid DEA registration that includes Schedule III authority, and be authorized to prescribe buprenorphine in the state in which they deliver care. (SAMHSA, 2023).

The **Mainstreaming Addiction Treatment Act** (also known as the "MAT Act") of 2023 removed the federal requirement that practitioners apply for a special waiver prior to prescribing buprenorphine for the treatment of opioid use disorder. The act also removed other federal requirements, including discipline restrictions, patient limits, and certification related to the provision of counseling (SAMHSA, 2023-b).

The **Drug Enforcement Administration (DEA)** enforces laws and regulations for controlled substances, including those pertaining to buprenorphine-containing products approved by the FDA for the treatment of OUD.

The **Food and Drug Administration (FDA)** requires a **Risk Evaluation and Mitigation Strategy (REMS)** program for buprenorphine extended-release injection, which is exclusively available through a restricted distribution process. The goal of REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration of buprenorphine extended-release injection.

There are two pathways for ordering buprenorphine extended-release injection: **buy-and-bill** and **specialty pharmacy.**

- Organizations utilizing the **buy-and-bill** system procure buprenorphine extended-release injection in bulk directly from a network specialty pharmacy and arrange bulk delivery to their site. This approach necessitates that the organization be REMS-certified, meeting specific criteria for that medication. While it allows the organization to maintain a stock of buprenorphine extended-release injections, it also entails upfront payment for the medication, which assumes the risk of any medication not covered by insurance. Upon administering the medication to a patient, the organization submits a claim to the patient's insurance for reimbursement. This reimbursement is processed as a medical benefit and may not appear on the state prescription drug monitoring program (PDMP) website, depending on the state's regulations.
- Organizations utilizing the **specialty pharmacy** system order buprenorphine extended-release injections by sending a prescription for a specific patient to an approved REMS-certified specialty pharmacy specific to the patient's insurance. The prescription is then delivered to the address listed on the prescriber's DEA license. A prescriber must possess a separate DEA number for each prescribing address if affiliated with multiple sites. Notably, the organization itself does not need to be REMS-certified in this process. The patient's insurance carrier determines the choice of specialty pharmacy, leading organizations to often coordinate with multiple specialty pharmacies. The specialty pharmacy directly bills the patient's insurance, and this appears as a pharmacy benefit on the state prescription drug monitoring program (PDMP) website.

Reverse Distribution is one method for handling controlled substances for the purpose of returning unwanted, expired, or damaged controlled substances to the manufacturer or arranging for disposal via incineration allowable by the DEA.

Implementing Buprenorphine Extended-Release Injection: Administrative Requirements

REQUIREMENT	ADDITIONAL INFORMATION	HELPFUL RESOURCES & REFERENCES
DEA Licensing & Prescribing ❑ DEA license for Schedule III substances for each site ❑ Organizational policies adherent to DEA, state, and location regulations for handling buprenorphine	• Each site within an organization handling controlled substances must have a separate DEA license for Schedule III medications. • When applying for or updating a DEA license, organizations must meet DEA security requirements, which may include site assessments or submitting facility blueprints. • The DEA may conduct unannounced site visits to ensure compliance with regulations for buprenorphine handling. • Buprenorphine prescribers must hold an active DEA license, and buprenorphine extended-release injection will be delivered to the prescriber's listed DEA address. • The registered address on a DEA license must match the physical location of one's primary place of business (not one's home address). Prescribers are required to have a distinct DEA license for *each site* where they prescribe buprenorphine extended-release injection.	DEA Forms and Applications (DEA, 2024b) Code of Federal Regulations: Title 21 – Chapter II – Part 1301 – Security Requirements (National Archives and Records Administration, 2023a)
Medication Storage & Tracking ❑ Secured, double-locked storage system ❑ *Refrigerator for storage if required by manufacturer.* ❑ Medication tracking log	• Buprenorphine tracking and handling requires a licensed healthcare provider (MD, DO, NP, PA, RN, LPN, pharmacist). • Organizations must follow DEA regulations for storing buprenorphine in a double-locked system, in addition to manufacturer storage guidelines. • If refrigeration is required, a pharmaceutical-grade refrigerator is preferred, with documented temperature monitoring. Refer to the manufacturer for specific storage guidelines. • Best practice entails medication logs signed by two licensed providers. Ensure compliance by following institutional standards, facility licensing requirements, and those related to the licensing of health care professionals.	DEA: Prescription Q&A (DEA, 2024) SAMHSA: Provider Support Services (SAMHSA, 2023a) DEA: Form 41 (DEA, 2024c)

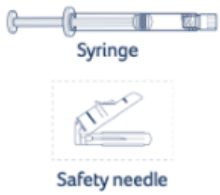
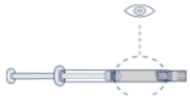
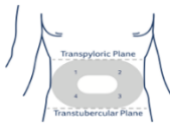
	• Accurate tracking of controlled substances safeguards healthcare workers and the public. Frequent reconciliations with another professional simplify resolving discrepancies.	
Medical Records ❑ Record storage adherent to DEA and state regulations ❑ *Adherence to 42 CFR regulations*	• Medical records must be kept for at least two years following DEA guidelines, and possibly longer per state rules. Electronic records are DEA-compliant. • Electronic prescribing is mandated by CMS and others for Schedule III-V meds. • 42 CFR Part 2 adds extra patient privacy measures within medical records for those seeking substance use disorder treatment.	Code of Federal Regulations: Title 21 - Chapter II - Part 1304 - Records and Reports of Registrants (National Archives and Records Administration, 2023c) Fact Sheet: SAMHSA 42 CFR Part 2 Revised Rule (SAMHSA, 2020)
Delivery Method: Buy and-Bill ❑ Policies adherent to REMS and DEA regulations	• Organizations using buy-and-bill must be REMS certified and use a network specialty pharmacy. • Medication is purchased in bulk directly from a network specialty distributor, and then patient's insurance is billed (as a medical benefit) only after administration of the medication.	FDA: Information on REMS for SUBLOCADE® (FDA, 2023-a) FDA: Information on REMS for BRIXADI® (FDA, 2023-b) SUBLOCADE® Risk Evaluation & Mitigation Strategy (REMS) (INDIVIOR, 2023) BRIXADI® Risk Evaluation and Mitigation Strategy (REMS) (Braeburn, 2023)

Delivery Method: Specialty Pharmacy ❑ Policies adherent to DEA regulations	• Organizations using a specialty pharmacy do not need to be REMS certified. • Medication is ordered for a specific patient through a specialty pharmacy (determined by insurance carrier) and billed as a pharmacy benefit. Specialty pharmacies will not accept medication returns after distributed and billed to an organization. **Medication that is patient-specific can only be stored onsite for 45 days after being received**, after which it needs to be disposed of following your organization's protocol.	DEA: Prescription Q&A (DEA, 2024)
Organizational Policies & Education ❑ Development of organization-specific policies and procedures for buprenorphine extended-release injection workflows. ❑ Training for healthcare team ❑ Assessing nursing competency	• Organization policies for on-site buprenorphine extended-release injection must align with DEA and REMS requirements. This includes storage, inventory, pharmacy coordination, patient tracking and monitoring, record-keeping, and security. • Training for team members, particularly nurses and providers, is critical for safe and appropriate use of buprenorphine extended-release injection. Topics include patient selection, medication administration and adverse effects, addressing missed appointments or continued substance use, and lab testing. • Adverse injection site reactions are most common with inadvertent intradermal or intramuscular administration of injectable buprenorphine. Proper administration technique is critical to minimizing these events and nursing competency should be assessed.	BMC Grayken Center for Addiction TTA Clinical Guidelines – Subsections on Buprenorphine extended-release injection (Wason et al., 2021) BMC Grayken Center for Addiction TTA Nursing Competencies – See Assessment (starts on p. 29) and Skills Checklists (starts on p. 44) (Wason et al., 2021)

BRIXADI® & SUBLOCADE® Clinical Tool

	SUBLOCADE®	BRIXADI®	
Prior to Starting	May be started after ≥8mg daily of transmucosal buprenorphine for at least 7 days	May be started after a single 4mg dose of transmucosal buprenorphine	
Packaging	Pre-filled syringe with 19-gauge, 5/8-inch needle	Pre-filled syringe with 23-gauge, 1/2-inch needle	
Storage	- Double lock system - Store refrigerated at 2°C to 8°C (35.6°F to 46.4°F). - Once outside refrigerator, may be stored at room temperature (15°C to 30°C; 59°F to 86°F), for up to 12 weeks.	- Double lock system - Refrigeration not required. - Store at room temperature at 20°C to 25°C (68°F to 77°F)	
Frequency	Administered monthly.	Available in weekly or monthly dosing formulations.	
Dosing	- First two loading doses: 300mg / 1.5mL - Maintenance doses: 100mg / 0.5mL Monthly maintenance dose may remain at or be increased to 300mg if inadequate clinical response.	<u>Weekly dosing:</u> - 8mg / 0.16mL - 16mg / 0.32mL - 24mg / 0.48mL - 32mg / 0.64mL	<u>Monthly dosing:</u> - 64mg / 0.18mL - 96mg / 0.27mL - 128mg / 0.36mL ***Weekly doses cannot be combined to yield an equivalent monthly dose.***
Steady State	4-6 months	Weekly formulation: 4 weeks Monthly formulation: 4 months	
Site of Administration	Administered subcutaneously in the abdomen only.	Administered subcutaneously in the buttock, thigh, abdomen, or upper arm*. **In patients new to weekly BRIXADI®, upper arm site should only be used after steady state achieved (4 consecutive doses).*	
Injection Angle	45-degree angle	90-degree angle	
Can depot be removed?	Yes, depot can be surgically removed within 14 days of administration.	No, depot cannot be removed once medication is administered.	
REMS Status	REMS required		
Use in Pregnancy	Use with caution	Use with caution. Avoid BRIXADI® injections in the abdomen during pregnancy.	
Warnings and Precautions	Risk of Hepatitis, Hepatic Events: Monitor liver function tests (LFTs) prior to and during treatment. Not recommended in moderate to severe hepatic impairment.		
		-**Latex allergy**: BRIXADI® needle cap is synthetically derived from natural rubber latex which may cause allergic reactions in latex-sensitive individuals. -**Soybean allergy**: BRIXADI® contains soybean and should not be used in those with a soybean allergy.	
Detectable Levels after Last Injection	Detectable plasma and urine levels (once steady state achieved) for 12 months or longer.	Detectable plasma levels (once steady state achieved): - Weekly formulation: Approximately 1 month - Monthly formulation: Approximately 4 months The correlation between BRIXADI® plasma concentrations and those detectable in urine is not known.	

SUBLOCADE® Administration

1. Getting Ready: Ensure medication has been ordered by prescriber and received on site. Confirm the medication dose and formulation. Check expiration date and document lot number. Do not remove from the carton until ready to administer. Remove the foil pouch and safety needle from the carton. Open pouch and remove syringe.	
2. Check the Liquid Clarity: Check that the medication does not contain contaminants or particles. SUBLOCADE® ranges in color from colorless to yellow to amber.	
3. Attach the Safety Needle: Remove the cap from the syringe and the safety needle supplied in the carton from its sterile package. Gently twist the needle clockwise until it is tight and firmly.	
4. Prepare the Abdominal Injection Site: Choose an injection site on the abdomen with adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment). It is recommended that patient is in supine position. Clean injection site with an alcohol swab. Rotate injection sites with each administration.	
5. Remote Excess Air from Syringe: Hold the syringe upright for several seconds to allow air bubbles to rise. Remove needle cover and slowly depress the plunger to push out the excess air from the syringe.	
6. Pinch the Injection Site: Pinch the skin around injection area. Be sure to pinch enough skin to accommodate the size of the needle. Lift adipose tissue from underlying muscle to prevent accidental intramuscular injection.	
7. Inject the Medication: Insert needle at a 45-degree angle fully into the abdominal subcutaneous tissue. Use a slow, steady push to inject the medication. Continue pushing until all the medication is given. Total volume: 0.5 ml. for 100 mg and 1.5 ml for 300 mg. SUBLOCADE® is for subcutaneous injection. • *Adverse injection site reactions are most common with inadvertent intradermal or intramuscular administration of injectable buprenorphine. Proper administration technique is critical to minimizing these events.*	
8. Withdraw the Needle: Withdraw needle at the same angle used for insertion and release the pinched skin. Do not rub the injection area after injection. There may be a small amount of blood or fluid at the injection site; wipe with a cotton ball or gauze before applying gauze pad or bandage using minimal pressure.	
9. Lock the Needle Guard and Discard the Syringe: Lock needle guard into place by pushing it against a hard surface such as a table. Dispose of syringe components in a secure sharps disposal container. After administration, syringes should be properly disposed, per facility procedure for a Schedule III drug, and per applicable federal, state, and local regulations.	
10. Instruct the Patient: Advise the patient that the lump on their abdomen will decrease in size over time. Instruct the patient not to rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands. Educate the patient about signs of injection site reaction and when follow-up would be needed.	

Adapted from Indivior (2023).

Consent for Treatment with SUBLOCADE®

Buprenorphine is a medication used to treat opioid use disorder. It is an opioid that reduces cravings and withdrawal symptoms and blocks the effects of stronger and more dangerous opioids to reduce overdose risk. Buprenorphine can be taken as a daily pill or film or as a subcutaneous (under the skin) injection. This consent form is about the monthly shot called SUBLOCADE®.

Buprenorphine can be used for withdrawal management or maintenance therapy. Opioid use disorder is a chronic condition, and maintenance therapy with buprenorphine can continue as long as medically necessary. Longer engagement in treatment is associated with better patient outcomes. It is recommended that buprenorphine treatment lasts for at least six (6) months.

SUBLOCADE® is an extended-release form of buprenorphine. SUBLOCADE® is administered every 28 days into the abdomen. It comes in two (2) different doses: 300mg and 100mg. The recommended dosing for the first two injections is 300mg. After the first two injections, the dose may be decreased to 100mg or can be continued at 300mg. Your clinical team will work with you to determine the most appropriate dose for you.

The patient information you need to know about SUBLOCADE® and its side effects is attached.
We will review that material with you before we ask you to sign this form for treatment.

I have read this form and the patient medication form or had them read to me. I understand what they say. I was given the opportunity to ask questions. All of my questions were answered. I believe I have enough information to consent to the SUBLOCADE® shot. By signing this form, I authorize my clinical team to perform subcutaneous injections of SUBLOCADE® in the abdomen as medically appropriate.

Patient Signature Date

Provider Signature Date

SUBLOCADE® Patient Education Sheet

This handout provides information on SUBLOCADE®, an injectable formulation of buprenorphine. Please read it and let your provider know if you have any questions.

What is SUBLOCADE®, and how does it work? SUBLOCADE® is a long-acting buprenorphine injection used to treat opioid use disorder. The injection is available in two doses (300 mg and 100 mg) and is administered every 28 days.

- SUBLOCADE® gives you an entire month of medicine in one injection. It continuously releases medicine at steady levels without daily highs and lows.
- The manufacturer recommends initiating SUBLOCADE® with a loading dose of 300 mg for the first two months. For maintenance, individuals can continue the 300 mg dose or decrease to the 100 mg dose.

What do I need to do before starting SUBLOCADE®? Before starting SUBLOCADE®, you must tolerate ≥8 mg daily of transmucosal buprenorphine for at least 7 days.

- If you are currently using opioids and not taking buprenorphine, work with your provider to start buprenorphine films or tabs first to avoid precipitated withdrawal prior to receiving the injection.

How will I get my SUBLOCADE® injections?

- SUBLOCADE® will be administered by your healthcare provider as a subcutaneous injection (under the skin) in your stomach (abdomen).
- SUBLOCADE ® is injected as a liquid that forms a lump under the skin called a depot. You may see or feel a small bump under your skin at the injection site for several weeks, which may get smaller over time. Do not try to remove the depot.

What are the possible side effects of SUBLOCADE®? Like any medicine, SUBLOCADE® may cause side effects. The most common side effects are:

- Headache
- Constipation
- Nausea/Vomiting
- Fatigue
- Increased liver enzymes

Injection-site adverse reactions are typically mild to moderate. Still, please contact your healthcare team immediately if you experience increased pain, redness, skin changes, or burning/itching of the injection site, as this may warrant further evaluation.

Contact your health care team or seek care immediately if you think you may be experiencing any other severe side effects, such as trouble breathing, sleepiness, dizziness or problems with coordination, liver problems (dark urine, yellow skin/eyes, abdominal pain), allergic reaction, opioid withdrawal, or low blood pressure.

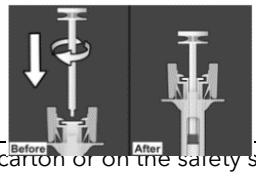
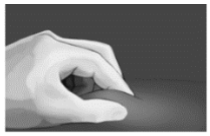
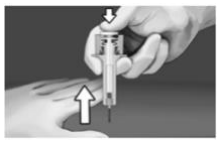
What is the important safety information I need to know about SUBLOCADE®?

SUBLOCADE® should never be injected into a vein because it would cause serious harm or even death. Patients should never handle this medication.

Death or serious harm can happen if you take anxiety medicines or benzodiazepines, sleeping pills, tranquilizers, muscle relaxers or sedatives, or drink alcohol during treatment with SUBLOCADE®. In an emergency, you or your family should tell the medical staff you are on SUBLOCADE®.

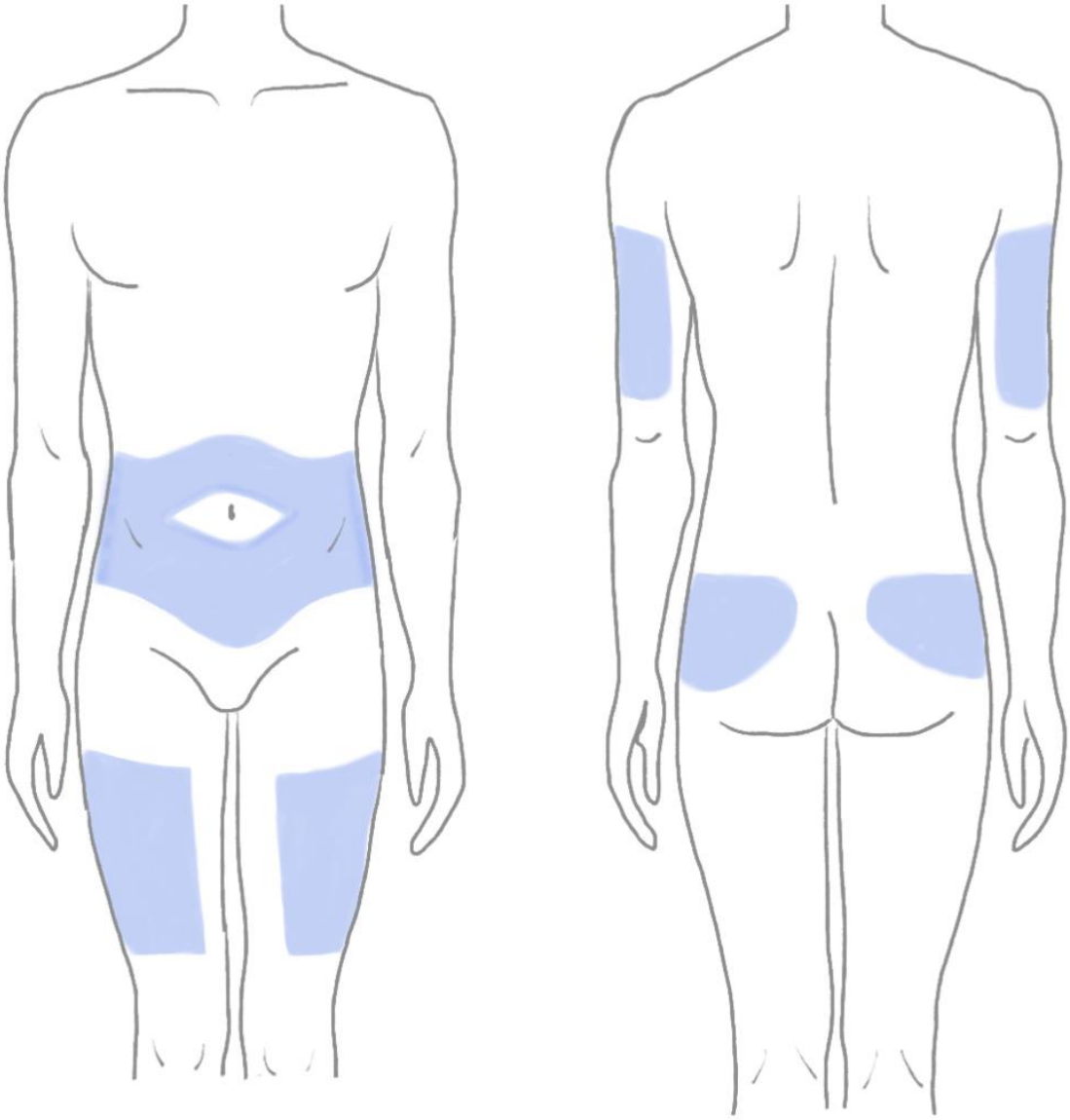
Ask your healthcare provider about naloxone (Narcan®) —a medication that reverses an opioid overdose.

BRIXADI® Administration

1. **Getting Ready**: Ensure medication has been ordered by prescriber and received on site. Confirm the medication dose and formulation. Check expiration date and document lot number. Do not remove from the carton until ready to administer. Remove the foil pouch and safety needle from the carton. Open pouch and remove syringe.	
2. **Inspect Safety Syringe**: Do not use the safety syringe after the expiration date shown on the carton or on the safety syringe label.	
3. **Check Liquid Clarity**: The liquid should be clear, and yellowish in color. A small air bubble may be visible. Do not use the safety syringe if the liquid contains visible particles or is cloudy.	
4. **Prepare Injection Site**: Choose an injection site (either abdomen, thigh, buttock, or upper arm) with adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment). Clean injection site with an alcohol swab.	
5. **Prepare the Safety Syringe**: Grasp the safety syringe by the syringe. Carefully pull needle cap straight off. Immediately dispose of needle cap; never try to recap the needle. It is normal to see a small drop of liquid at tip of the needle.	
6. **Pinch the Injection Site**: Pinch the skin at the injection site between your thumb and index finger.	
7. **Inject the Medication**: Insert needle at a 90-degree angle fully into the subcutaneous tissue. After the needle is completely inserted, release the skin that you are grasping. Slowly press down the plunger head until it latches in the safety device 'wings.' This will ensure all the medication has been injected. Keep the plunger pressed fully down while you hold the safety syringe in place for an additional 2 seconds. • *Adverse injection site reactions are most common with inadvertent intradermal or intramuscular administration of injectable buprenorphine. Proper administration technique is critical to minimizing these events.*	 
8. **Withdraw the Needle**: Gently pull the needle out of the skin. Keep the plunger fully depressed while you carefully lift the needle straight out from the injection site.	
9. **Activate the Safety Guard and Discard the Syringe**: As soon as you have completely removed the needle from the skin, slowly take your thumb off the plunger. Allow the syringe guard to automatically cover the exposed needle. There may be a small amount of blood at the injection site. If needed, wipe with a cotton ball or gauze. Dispose of syringe components in a secure sharps disposal container.	
10. **Instruct the Patient**: Advise patient the lump on their abdomen will decrease in size over time. Instruct the patient not to rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands. Educate the patient about signs of injection site reaction and when follow-up would be needed.	

Adapted from Braeburn (2023)

Administration Sites for BRIXADI®



**When administering BRIXADI® Weekly, the upper arm site should only be used after a steady state has been achieved (4 consecutive doses). Injection in the arm site is associated with approximately 10% lower plasma levels (Braeburn, 2023).*

Consent for Treatment with BRIXADI®

Buprenorphine is a medication used to treat opioid use disorder. It is an opioid that reduces cravings and withdrawal symptoms and blocks the effects of stronger and more dangerous opioids to reduce overdose risk. Buprenorphine can be taken as a daily pill or film or as a subcutaneous (under the skin) injection. This consent form is about the monthly shot called BRIXADI®.

Buprenorphine can be used for withdrawal management or maintenance therapy. Opioid use disorder is a chronic condition, and maintenance therapy with buprenorphine can continue as long as medically necessary. Longer engagement in treatment is associated with better patient outcomes. It is recommended that buprenorphine treatment lasts for at least six (6) months.

BRIXADI® is an extended-release form of buprenorphine that has two (2) formulations: a weekly injection and a monthly injection.

- BRIXADI® weekly is administered every 7 days. It comes in four (4) different doses: 8mg, 16mg, 24mg, and 32mg.
- BRIXADI® monthly is administered every 28 days. It comes in three (3) different doses: 64mg, 96mg, and 128mg.

Your clinical team will work with you to determine the most appropriate formulation (weekly or monthly) and dose for you. Both formulations of BRIXADI® can be administered subcutaneously in one of four (4) areas: abdomen, buttock, thigh, or upper arm.

The patient information you need to know about BRIXADI® and its side effects is attached.
We will review that material with you before we ask you to sign this form for treatment.

I have read this form and the patient medication form or had them read to me. I understand what they say. I was given the opportunity to ask questions. All of my questions were answered. I believe I have enough information to consent to the BRIXADI® shot. By signing this form, I authorize my clinical team to perform subcutaneous injections of BRIXADI® into one of four locations—abdomen, buttock, thigh or upper arm—as medically appropriate.

Patient Signature Date

Provider Signature Date

BRIXADI® Patient Education Sheet

This handout provides information on BRIXADI®, an injectable formulation of buprenorphine. Please read it and let your provider know if you have any questions.

What is BRIXADI®, and how does it work? BRIXADI® is a long-acting buprenorphine injection used to treat opioid use disorder. The injection is available in two formulations: weekly and monthly.

Weekly BRIXADI® administered every 7 days	Weekly doses: 8mg, 16mg, 24mg, 32mg
Monthly BRIXADI® administered every 28 days	Monthly doses: 64mg, 96mg, 128mg

- BRIXADI® gives you an entire week or month of medicine in one injection by continuously releasing medicine all week or month at steady levels without daily highs and lows. Your healthcare team will work with you to determine the appropriate formulation and dose for you.

What do I need to do before starting BRIXADI®?

- Before starting BRIXADI®, you must be able to tolerate at least ONE 4 mg dose of transmucosal buprenorphine OR are already taking buprenorphine.
- If you are not currently taking buprenorphine, you will need to start with weekly BRIXADI®.
- If you are already on buprenorphine, you can start with either weekly or monthly BRIXADI®.
- If you are currently using opioids and not taking buprenorphine, work with your provider to start buprenorphine films or tabs first to avoid precipitated withdrawal prior to receiving the injection.

How will I get my BRIXADI® injections?

- BRIXADI® will be administered by your healthcare provider as a subcutaneous injection (under the skin) in either your buttock, thigh, stomach (abdomen) or upper arm.
- BRIXADI® is injected as a liquid that forms a lump under the skin called a depot. For a few weeks, you may see or feel a small bump under your skin at the injection site, and it may get smaller over time. Do not try to remove the depot.

What are the possible side effects of BRIXADI®?

Like any medicine, BRIXADI® may cause side effects. The most common side effects are:

- Headache
- Constipation
- Nausea
- Trouble sleeping (insomnia)
- Urinary tract infection

Injection-site adverse reactions are typically mild to moderate. Still, please contact your healthcare team immediately if you experience increased pain, redness, skin changes, or burning/itching of the injection site, as this may warrant further evaluation.

Contact your health care team or seek care immediately if you think you may be experiencing any severe side effects, such as trouble breathing, sleepiness, dizziness or problems with coordination, liver problems (dark urine, yellow skin/eyes, abdominal pain), allergic reaction, opioid withdrawal, or low blood pressure.

What is the important safety information I need to know about BRIXADI®?

BRIXADI® should never be injected into a vein because it would cause serious harm or even death. Patients should never handle this medication. Death or serious harm can happen if you take anxiety medicines or benzodiazepines, sleeping pills, tranquilizers, muscle relaxers or sedatives, or drink alcohol during treatment with BRIXADI®. The BRIXADI® needle cap is made with latex and may cause sensitivity in latex-allergic individuals. BRIXADI® contains soybeans, so those with a soybean allergy should avoid this medication. In an emergency, you or your family should tell the medical staff you are on BRIXADI®.

Ask your healthcare provider about naloxone (Narcan®) —a medication that reverses an opioid overdose.

Disposal of Buprenorphine Extended-Release Injection

Buprenorphine extended-release injections that are expired, damaged, or unwanted must be reverse distributed or destroyed and disposed of following DEA rules and regulations described in Title 21 CFR Part 1330 (Electronic Code of Federal Regulations, 2024). The disposal of buprenorphine extended-release injections involves specific DEA regulations to maintain a closed distribution system, including disposal within 45 days of receipt of medication. 21 Code of Federal Regulations (CFR) Part 1317 reviews these requirements.

DEA regulations for destroying, disposing, or "wasting" Schedule III medications require rendering the controlled substance "non-retrievable," meaning the substance is permanently changed to an unusable state. Mixing controlled substances with undesirable items (e.g., kitty litter or coffee grounds) or flushing down a toilet or sink does not meet DEA non-retrievable standards. Once a substance is properly destroyed and becomes non-retrievable, it is no longer subject to the DEA's regulations because it cannot be misused or diverted for illicit use as it would be ineffective (Electronic Code of Federal Regulations [Title 21 CFR Part 1317], 2024).

The method of how your site orders and obtains buprenorphine extended-release injection (buy-and-bill vs specialty pharmacy), along with organization-specific policies and procedures, may influence the chosen method for managing unused controlled substances following state and federal regulations. Specialty pharmacies are prohibited from accepting returns of buprenorphine extended-release injections once they have been dispensed to your clinic or office due to the inability to verify the medication's integrity. In this case, your site is responsible for the disposal of the medication. When buprenorphine extended-release injection is obtained through the "buy and bill" process, the specialty distributor may be able to assist you in coordinating reverse distribution with a third-party vendor.

Reverse Distribution

A reverse distributor is a DEA-registered entity legally allowed to handle controlled substances for the purpose of returning unwanted, expired, or damaged substances to the manufacturer or arranging for disposal via incineration. Reverse distribution of controlled substances can be facilitated through a DEA-registered reverse distributor or through the medication manufacturer (typically only offered with buy-and-bill).

Reverse distribution is most often provided in one of two ways:

- **On-site collection**: The reverse distributor travels to your site to take care of the packaging and carrier pickup of the medication and reviews paperwork to ensure compliance.
- **Mail-back program:** The reverse distributor provides you with prepaid shipping labels. Your organization completes the necessary regulatory forms, packages the medication, and then ships the product to the reverse distributor for destruction.

Before contacting a reverse distributor, you should check with your organization's pharmacy or facilities department to see if they already have a contract with one. Some companies that dispose of hazardous waste may also dispose of controlled substance waste. Contact your Local DEA Diversion Field Office for assistance finding a DEA-registered reverse distributor.

Methods for Rendering a Substance "Non-Retrievable"

Incineration and chemical digestion are two DEA-approved methods for rendering a substance destroyed and non-retrievable. Due to incineration's cost and logistical complications, this method is typically reserved for hazardous waste material through smaller practices and organizations. Chemical digestion involves putting the controlled substance in a cartridge, pouch, or bottle that contains a chemical (e.g., carbon, bentonite clay, or calcium hypochlorite) that deactivates, neutralizes, or breaks down the medication, rendering its ingredients inert.

The DEA and the Environmental Protective Agency (EPA) have not endorsed a specific chemical digestion product. Various commercially available chemical digestion systems meet DEA standards for rendering controlled substance medication in pill and/or liquid form non-retrievable. Industry best practice is using a specially designed pharmaceutical receptacle that renders the controlled substance non-retrievable and partnering with a waste management vendor to remove, process, or incinerate the waste containers.

An organization-specific policy (Appendix D) for destroying and disposing of irretrievable long-acting buprenorphine extended-release injections should be implemented to ensure safety and adherence to DEA guidelines.

Documentation and Record Keeping

The DEA requires organizations to maintain a record of the destruction of controlled substances, including buprenorphine extended-release injection, using DEA Form 41 (Appendix C). Additionally, the regulations state that the record of the medication should be "complete and accurate and include the name and signatures of the two licensed employees who witnessed the destruction" (Electronic Code of Federal Regulations, 2024). The DEA reinforces the importance of two employees witnessing the medication destruction and disposal in addition to appropriate documentation, including signatures (Electronic Code of Federal Regulations, 2024).

You are not required to submit Form 41 to the DEA unless requested to do so. This form must be kept for at least two years, or longer if required by state law, in addition to controlled substances logs. The best practice is to standardize the documentation of destruction and disposal of buprenorphine extended-release injection.

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Appendix A: Ordering Buprenorphine Extended-Release Injections

Appendix A provides a tool for differentiating the two pathways for ordering buprenorphine extended-release injections: **buy-and-bill** and **specialty pharmacy.**

A1. Buy and Bill vs. Specialty Pharm Clinical Tool

	Specialty Pharmacy	Buy and Bill
Type of Benefit	Pharmacy benefit	Medical benefit
REMS (Risk Evaluation and Mitigation Strategy) Certification	If ordering through a specialty pharmacy, the specialty pharmacy must be REMS-certified. Your healthcare setting does not need to be REMS certified if ordering through this process.	If ordering through a specialty distributor, your healthcare setting must be REMS-certified. To enroll in medication-specific REMS, go to: • SUBLOCADE® REMS • BRIXADI® REMS
Where to Obtain Medication	• Certified pharmacy locator for SUBLOCADE® • Certified pharmacy locator for BRIXADI®	Your healthcare setting must set up an account with a network specialty distributor: • Network Specialty Distributor - SUBLOCADE® • Network Specialty Distributor - BRIXADI®
How to Obtain Medication	Your office sends a valid prescription to the specialty pharmacy and the pharmacy determines coverage for the patient. Prior Authorization (PA) and/or co-pay may be required. Once medication is approved, specialty pharmacy works with your office to coordinate shipment. The pharmacy may contact patient to confirm the medication prior to shipping.	Your office must first determine the patient's coverage for the medication. Once coverage is determined, the medication is ordered and purchased directly from a specialty distributor. Prior Authorization (PA) and/or co-pay may be required.
	There may be out-of-pocket expenses associated with injectable buprenorphine. Explore co-pay assistance programs for patients.	
Submitting a Claim	After the medication has been administered, your office submits a claim to the patient's health insurance.	After the medication has been administered, your office submits a claim to the patient's health insurance. If the claim is approved, the payer should provide payment.
PDMP Status	Will show up on the state PDMP	May *NOT* show up on the state PDMP
Disposal of Unused or Expired Medication	Specialty pharmacies are prohibited from accepting returns once medication has been dispensed due to the inability to verify the medication's integrity. Your healthcare setting will need to dispose of the medication in one of two ways: (1) on-site chemical digestion OR (2) reverse distribution through a third party.	Manufacturers may offer a reverse distribution program through a third-party vendor; contact the manufacturer directly for more details. • Indivior (SUBLOCADE®): 1-877-782-6966 • Braeburn (BRIXADI®): 1-833-274-9234

Appendix B: TTA Resources for Buprenorphine Extended-Release Injection

Appendix B details the resources Boston Medical Center's Grayken Center for Addiction Training & Technical Assistance provides. Resources may be found at addictiontraining.org and are hyperlinked below.

B1. Buprenorphine Extended-Release Injection Resources

- Clinical Guidelines
- Patient Consent for Treatment with SUBLOCADE® and BRIXADI® (visit our website for consents in other languages)
- Patient Medication Guide – to provide to patients at the time of signed consent.
- Administration Checklist – provides detailed steps for administering buprenorphine extended-release injectable formulations.
- Protocol for Lidocaine Administration Prior to Extended-Release Buprenorphine Injection
- Injection Video – demonstration of procedures for administering SUBLOCADE® in the clinic setting.

B2. Buprenorphine Extended-Release Injection Trainings

Filter the Category by "Buprenorphine," and any scheduled trainings will appear.

B3. Nursing Competencies

See the Assessment Document and the Skills Checklist.

Appendix C: Medication Tracking

Appendix C provides tools for medication tracking, including the DEA Form 41, a Buprenorphine Tracking log, and a Buprenorphine Disposal Log.

C1. DEA Form 41

The U.S. Drug Enforcement Administration requires the completion of DEA Form 41 to record controlled substance destruction. This form must be kept and available for a minimum of two years in compliance with 21 U.S.C. 827.

C2. Buprenorphine Tracking Log

BUPRENORPHINE EXTENDED-RELEASE MEDICATION TRACKING LOG							
Patient name, DOB, MRN	**Medication Formulation & Dose**	**Lot #**	**Exp. Date**	**Received from pharmacy or distributor Signatures & Date**	**Removed from refrigerator or med box Signatures & Date**	**Returned to refrigerator or med box** (If med not administered) **Signatures & Date**	**Removed from refrigerator or medication box. Signatures & Date**
				1. 2.	1. 2.	1. 2.	1. 2.
				1. 2.	1. 2.	1. 2.	1. 2.
				1. 2.	1. 2.	1. 2.	1. 2.
				1. 2.	1. 2.	1. 2.	1. 2.

C3. Buprenorphine Disposal Log

DISPOSAL OF BUPRENORPHINE EXTENDED-RELEASE LOG							
Patient name, DOB, MRN	**Medication formulation and Dose**	**Lot #**	**Exp. Date**	**Reason for Disposal (expired, unwanted, damaged, etc.)**	**Method of Disposal: Destruction or Reverse Distribution**	**Destruction**	**Reverse Distribution**
						□ Method and date of destruction:	□ Name of reverse distributor used and date:
						□ Signatures & printed names of 2 licensed employees witnessing destruction:	□ Signatures & printed names of 2 licensed employees witnessing reverse distribution:
						1. 2.	1. 2.
						□ Document in patient's chart □ DEA Form 41 completed	□ Document in patient's chart
						□ Method and date of destruction:	□ Name of reverse distributor used and date:
						□ Signatures and printed names of 2 licensed employees who witness the destruction:	□ Signatures and printed names of 2 licensed employees who witness reverse distribution:
						1. 2.	1. 2.
						□ Document in patient's chart □ DEA Form 41 completed	□ Document in patient's chart

Appendix D: Policy for On-Site Destruction of Extended-Release Injectable Buprenorphine

Appendix D provides Boston Medical Center's established policy for on-site destruction of extended-release injectable buprenorphine, including a step-by-step procedure for destruction and documentation requirements.

D1. On-Site Destruction of Extended-Release Injectable Buprenorphine

Purpose

This policy establishes standard procedures for properly handling and safely disposing of damaged, expired, recalled, unused, or unwanted extended-release injectable buprenorphine stored in ambulatory clinics.

Policy Statement

Boston Medical Center (BMC) has established a process to ensure that any damaged, expired, recalled, unused, or otherwise unwanted extended-release injectable buprenorphine is destroyed in compliance with applicable Federal, State, tribal, and local laws and regulations.

The Drug Enforcement Administration (DEA) requires that controlled substances be rendered "non-retrievable" during the disposal process. This means the substance's physical or chemical condition or state has been permanently altered through irreversible means, rendering it unavailable and unusable for all practical purposes. Once a substance is rendered non-retrievable, it is no longer subject to the requirements of the DEA regulations.

Application

BMC ambulatory clinics and affiliated community health centers

Exceptions

None

Procedure

A. On-site Method of Destruction

BMC opts for on-site destruction of extended-release injectable buprenorphine, meaning that the medication is destroyed on the physical premises of the clinic location.

BMC utilizes the DEA-approved destruction method of chemical digestion, a process that *renders extended-release injectable buprenorphine neutralized by the use of chemical reactions of a dissolving agent* combined with carbon.

"Approved Storage & Waste Hauling Inc" is the current vendor used by BMC for this destruction process. The vendor provides a secure, wall-mounted neutralization system (see image below). The 1.5 or 3-gallon waste container is secured to the wall by an external bracket or cabinet encloser depending on your needs. Once extended-release injectable buprenorphine is expelled or deposited into the container, the substance is immediately rendered non-retrievable or otherwise unfit for redistribution by the non-toxic neutralizer contained within.

B. Collection Receptacles

Collection receptacles for the disposal of extended-release injectable buprenorphine shall be securely placed and maintained. Collection receptacles shall be located in an area regularly monitored by employees and shall not be located in the proximity of any area where emergency or urgent care is provided.

A controlled substance collection receptacle shall meet the following design specifications (the receptacle provided by Approved Storage and Waste Hauling Inc meets these requirements):

- Be securely fastened to a permanent structure so that it cannot be removed.
- Be a securely locked, substantially constructed container with a permanent outer container and a removable inner liner.
- The outer container shall include a small opening that allows contents to be added to the inner liner, but does not allow removal of the inner liner's contents.
- The outer container shall prominently display a sign indicating that only Schedule II–V controlled and non-controlled substances, if a collector chooses to comingle substances, are acceptable substances.
- The small opening in the outer container of the collection receptacle shall be locked or made otherwise inaccessible to the public when an employee is not present (e.g. when the clinic is closed).

C. Witnessing Destruction

1. Two authorized employees (e.g. physician, advanced practice provider, registered nurse, licensed practical nurse, registered pharmacist, or pharmacy technician) shall handle or observe the handling of extended-release injectable buprenorphine until the substance is rendered non-retrievable; and
2. Two authorized employees shall personally witness the destruction of extended-release injectable buprenorphine until it is rendered non-retrievable.

D. Steps of Destruction

The following steps should be taken when rendering a substance non-retrievable:

1. Remove extended-release injectable buprenorphine from its packaging.
2. Waste the contents of the medication into the container provided by Approved Storage & Waste Hauling Inc and ensure the syringe is fully empty.
3. Dispose of any empty syringes, sharps, needles, and empty ampules into an approved sharps container.

Once extended-release injectable buprenorphine has been deposited into a collection receptacle, the substance shall not be counted, sorted, inventoried, or otherwise individually handled.

When the container has reached capacity, the receptacle is disposed of by a waste management vendor to remove and process the waste containers.

E. Documenting Destruction

The destruction of extended-release injectable buprenorphine must be documented on an appropriate controlled substance log that records the date, location, medication formulation, dose and amount destroyed, method of destruction, and signature of two authorized employees.

The DEA also requires that organizations maintain a record of the destruction of controlled substances, including extended-release injectable buprenorphine, using DEA Form 41. You are not required to submit this form to the DEA, unless requested to do so.

The witness log and DEA Form 41 must be kept on-site for at least 2 years, or longer per state regulations.

Responsibility

Physicians, Advanced Practice Providers, Registered Nurses, Licensed Practical Nurses, Registered Pharmacists, Pharmacy Technicians

Forms

DEA Form 41

Related Policies

13.03.900 – Controlled Substance Quality Assurance
13.03.910 – Controlled Substance Proactive Diversion Monitoring and Investigation
13.03.940 – Controlled Substances in Clinics and Procedural Areas without an Automated Dispensing System (ADS)
13.80.440 – Pharmacy-Supplied Clinic-Administered Medication Storage and Disposal

Initiated by

BMC Office-Based Addiction Treatment (OBAT) Clinic.