**Buprenorphine extended-release Injection (Sublocade®)**
Schedule III Controlled Substance
FDA approved November 2017

**Indication**: Treatment of moderate to severe opioid use disorder (OUD) among patients initiated and taking transmucosal buprenorphine containing product for at least 1 week

**Mechanism of Action**: Buprenorphine displays partial mu agonist (with high-affinity binding to mu opiate receptors) & weak kappa antagonist activity.

**Dosage & Administration**

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| **Dosage** | ▪ Two initial monthly doses of 300mg SQ followed by 100mg monthly maintenance dose<br>▪ Maintenance dose may be increased to 300 mg monthly for clts with unsatisfactory clinical response<br>▪ Max dose: 300 mg per month<br>▪ Doses should be separated by at least 26 days |
| **Moderate to severe hepatic impairment** | ▪ Use not recommended |
| **Administration** | ▪SQ injection in the abdominal region by a healthcare provider in a health care setting. Rotate injection site with each injection & record the location in the medical record |
| **How Supplied** | ▪ 100mg/0.5mL and 300mg/1.5mL injection (prefilled syringe) |

**Drug Drug Interactions**

| Concomitant Medication | Effect |
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| CYP3A4 Inhibitors & Inducers | Monitor for potential over or under dosing |
| Serotonergic Drugs | Concomitant use may result in serotonin syndrome (lower risk compared to methadone). Monitor specially during treatment initiation & dose adjustment of serotonergic drugs |
| Antiretrovirals | Monitor clts on chronic buprenorphine if NNRTIs are added<br>Monitor clts on buprenorphine & atazanavir (with or without ritonavir). Dose reduction of buprenorphine may be necessary |
| Benzodiazepines & other CNS depressants | Additive effects, educate clts against concomitant self-administration/misuse, increased r/o respiratory depression, sedation, coma, & death |

**Adverse Effects**

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| Most frequently reported AEs | Constipation, headache, nausea, injection site pruritus/pain, vomiting, increased hepatic enzymes, & fatigue |

**Limitations of use**: Use is limited under the Drug Addiction Treatment Act. Healthcare settings and pharmacies must be certified in the Sublocade REMS Program and only dispense the medication to a provider for administration

## Warnings & Precautions

Black Box Warning: Risk of serious harm or death with IV administration. Available through a restricted Sublocade REMS Program only. Healthcare settings and pharmacies that order/dispense buprenorphine ER Injection must be certified and comply with REMS requirements

Other warnings & precautions

- Addiction, abuse, and misuse
- Respiratory depression
- Neonatal opioid withdrawal syndrome
- Adrenal insufficiency
- Risk of opioid withdrawal with abrupt discontinuation
- Risk of hepatitis, hepatic events
- Risk of withdrawal in patients dependent on full opioid agonists
- Treatment of emergent acute pain

## Pharmacokinetics

- The injectable depot formulation contains buprenorphine dissolved in a biodegradable delivery system using Atrigel® technology that releases buprenorphine at a controlled rate over a one month period

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| Tmax | 24 hours |
| Metabolism | Primarily hepatic via N-dealkylation by CYP3A4 & glucuronidation |
| Half-life | 43-60 days |
| Excretion | Feces (69%), urine (30%) |
| Duration of action | 28 days |
| Steady state | Achieved 4-6 months after therapy initiation. Average plasma buprenorphine concentrations are ~ 10% higher with SQ formulation vs 24 mg/day SL buprenorphine tabs |

## Clinical Studies

Efficacy: The efficacy of buprenorphine ER injection was evaluated in a 24-week, randomized, double-blind, placebo-controlled study in treatment-seeking patients with moderate or severe opioid use disorder. 504 patients were randomized to once-monthly 300 mg doses (n=203), monthly 300 mg doses followed by 4 monthly 100 mg doses (n=201), or monthly SQ injections of placebo (n=100). All subjects received manual-guided psychosocial support at least once a week. Prior to the first dose, treatment was initiated with buprenorphine/naloxone SL film & doses were adjusted over 7-14 days. Subjects were randomized after cravings and withdrawal symptoms were clinically controlled. Efficacy was assessed based on weekly urine drug screens & self-reported use of illicit opioid use. Buprenorphine injection was found superior & the proportion of subjects achieving treatment success (≥80% opioid-free weeks after the first SQ dose during weeks 5 to 24) was statistically significantly higher in both groups receiving buprenorphine injection vs placebo (29%, 28% vs 2%)

Safety: Injection site reactions (pain, pruritus, erythema, induration) were reported in 16.5% of subjects receiving buprenorphine ER injection (vs 9 % placebo). Headache, constipation, nausea, fatigue, somnolence, sedation, dizziness, & elevated hepatic enzyme were also reported more frequently compared to placebo.
An interim analysis of the 12-month open-label safety study (N=669) showed similar to the double blind trial adverse event profile

**Role in Therapy**

- The once-monthly SQ formulation of buprenorphine (granted priority review) appears to be effective for treatment of moderate to severe opioid use disorder
    - a new treatment option that may reduce nonadherence & diversion
    - buprenorphine appears to significantly improve treatment retention & reduces illicit opioid use compared to placebo
    - appears to be at least as effective as methadone in reducing mortality
    - unlikely to prolong the QT interval
    - Sublocade is however more expensive, has not been compared with other treatment options such as methadone, naltrexone, or other buprenorphine formulations in clinical trials
- Using alcohol, benzos or other CNS depressants with ER buprenorphine may lead to drowsiness/overdose
- Monitoring parameters include periodic hepatic enzyme tests, injection-site infection & evidence of attempts to tamper with/remove the depot. Monitor for S/Sx of withdrawal if treatment is discontinued
- Acute pain should be managed with non-opioid analgesics. Higher than usual opioid doses may be required if necessary to provide adequate analgesia
- Since buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa receptor, it displays a ceiling on its respiratory depressant effect. The risk of overdose and abuse may be lower compared to full opioid agonists
- Clt education
    - a lump may develop at the injection site for a few weeks that gradually reduces in size. Educate clts not to rub or massage the lump
    - IV self-injection can cause death
- Depots can be surgically removed under local anesthesia within 14 days of injection, if needed
- The ER buprenorphine injection should be used in conjunction with a comprehensive treatment program that includes counseling & psychosocial support
- Healthcare settings and pharmacies must receive Sublocade REMS Program certification and can only dispense the medication directly to healthcare providers for subcutaneous abdominal injection only by a healthcare provider
- Post-marketing studies include feasibility of administering the SQ buprenorphine at a longer inter-dose interval, transitioning patients stable on transmucosal buprenorphine to monthly injection without the use of a higher dose for the first two months, assessment of patients who would benefit from a higher dosing regimen, and if SQ injections can be safely started without a dose stabilization period of SL buprenorphine

- Manufacturer – “We will be offering a SUBLOCADE co-pay assistance program, and also a SUBOXONE® (buprenorphine and naloxone) Sublingual Film co-pay assistance program, that may reduce initial out-of-pocket costs for eligible patients to as little as $5 each month.” The Insupport Copay Assistance Program is for pts with private insurance only
- Please see attached fact sheet for information about how to obtain Sublocade

**Formulary recommendation**:
HPSM MediCal: carved out to State MC
CMC: PA required
BHRS Indigent: NF with approval criteria same as CMC below

APPROVAL CRITERIA

Covered Uses: All FDA-approved indications not otherwise excluded from Part D

Required Medical Information:

- Treatment plan that includes counseling or psychosocial support
- Stabilized on transmucosal buprenorphine for at least 7 days
- No concurrent opioids or carisoprodol or supplemental bruprenorphine while on Sublocade
- ONE of the following rationale for using injectable:
    - inability to take oral medications
    - nonadherence/noncompliance with oral medications
    - risk for diversion

Prescriber Restrictions: DATA-waived physicians with unique DEA number

Duration of Approval: 12 months; Quantity Limit: 300mg per 28 DS

**References:**


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