Review of Injectable Buprenorphine Products

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OUD ECHO Session June 2, 2021

Objectives

- Review Sublocade® and Brixadi™, including their efficacy and safety
- Discuss the benefits and setbacks with utilizing Sublocade®
- Evaluate when a patient would be a candidate for an injectable buprenorphine product

Sublocade®

Sublocade® Approval and Dosing

- Approved for moderate to severe opioid use disorder (OUD) in those who have initiated treatment with a transmucosal buprenorphine product for at least 7 days
- Dosing:
  - 300 mg dose for the first two months, then 100 mg monthly (may adjust to 300 mg maintenance)
- Missed dosing/Dosing windows:
  - No less than 26 days after previous dose
  - Delays in up to 2 weeks not expected to have significant impact
- Dose adjustments
  - None required for renal impairment, hepatic impairment, or in geriatric patient population

Sublocade [package insert]. North Chesterfield, VA: Indivior, Inc; 2017.

Sublocade® Administration

- Tmax at 24 hours post-injection
- Steady-state reached at 4 to 6 months
- Must be refrigerated
- Remove from fridge at least 15 minutes prior to administration
- Discard if left at room temperature for > 7 days
- Abdominal subcutaneous injection only
- Only administered by a HCP
- May remove surgically under local anesthesia within 14 days of injection
- Disposal: C-III agent requirements

Sublocade [package insert]. North Chesterfield, VA: Indivior, Inc; 2017.

Sublocade® Monitoring

Liver Function Tests (LFTs)

- Baseline
- Monthly (especially if 300 mg maintenance)

ECG monitoring (if at risk)

Efficacy monitoring

Monitoring for nursing

- Blood pressure, respiratory effects, sedation, GI effects, fall risk

Sublocade [package insert]. North Chesterfield, VA: Indivior, Inc; 2017.

Sublocade® REMS Program

- Exists due to risk of harm or death with intravenous administration
- Prescriber and pharmacy must be registered with REMS
- Must be administered by the HCP in office
- Product may not be dispensed directly to the patient
- Two options for dispensing:
  - Order directly from a distributor
  - Through a certified pharmacy for a specific patient

REMS= Risk Evaluation and Mitigation Strategy

Sublocade®. Risk evaluation and mitigation strategy (REMS). Available at: https://www.sublocaderems.com/

Brixadi™

Brixadi™ Approval and Dosing

- Tentatively approved for moderate to severe OUD in those who have initiated treatment with a single dose of transmucosal buprenorphine product
- Dosing:
  - Weekly or monthly dosing
    - Weekly doses: 8 mg, 16 mg, 24 mg, 32 mg
    - Monthly doses: 64 mg, 96 mg, 128 mg

Braeburn Inc. Available at: https://www.prnewswire.com/news-releases/fda-grants-braeburns-citizen-petition-allowing-brixadi-buprenorphine-extended-release-injection-for-opioid-use-disorder-to-be-available-in-december-2020-300954538.html

Additional Brixadi™ Dosing Information

- Weekly dosing:
  - 16 mg injection = 8 mg SL
  - 24 mg injection = 16 mg SL
  - 32 mg injection = 24 mg SL
- Monthly dosing:
  - 64 mg injection = 8 mg SL
  - 96 mg injection = 16 mg SL
  - 128 mg injection = 24 mg SL
  - 160 mg injection = 32 mg SL (in Phase 3 trial)
- Dosing windows per Phase 3 trials:
  - 2 days for weekly dosing
  - 7 days for monthly dosing

Efficacy and Safety

Sublocade® Efficacy (vs. Placebo)

Haight BR, Learned SM, et al. Efficacy and safety of monthly buprenorphine depot injection for opioid use disorder: A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial. Lancet 2019;393:778-90.	
Objective	• To assess the efficacy of two dosing regimens of monthly buprenorphine depot injection in individuals seeking treatment for OUD
Design	• Randomized, double-blind, placebo-controlled, multicenter phase 3 study

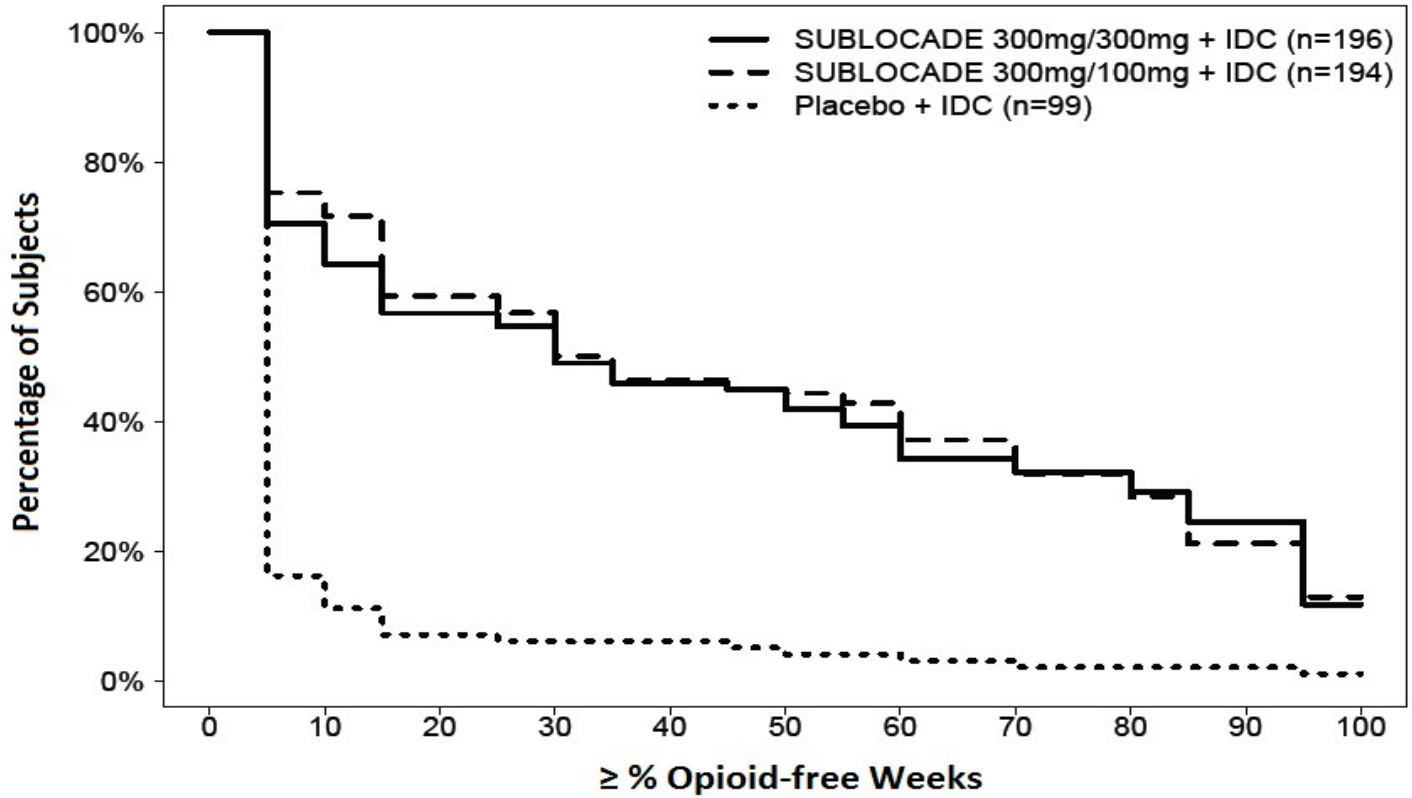
Methods	• 2 week open-label run-in phase with buprenorphine/naloxone sublingual films5 day buprenorphine-naloxone sublingual film taper that began on day 1 of BUP-XR or placebo
	• Dosing every 28 days
	  ○ BUP-XR 300/300 mg: 6 doses of 300 mg
	  ○ BUP-XR 300/100 mg: 2 doses of 300 mg, then 4 doses of 100 mg
	• Weekly visits for 24 weeks

Endpoints	• Primary:
	  ○ Percentage abstinence from opioid use
	  ▪ Defined as percentage of negative urine samples and self-report of illicit opioid use among 20 weekly opioid use assessments
	• Secondary:
	  ○ Treatment success
	  ▪ At least 80% opioid abstinence during weeks 5 to 24
	  ○ Treatment retention
	  ○ Clinical opiate withdrawal scale (COWS)
	  ○ Opioid craving visual analog scale (VAS) scores

Sublocade® Efficacy Results

Haight BR, Learned SM, et al. Efficacy and safety of monthly buprenorphine depot injection for opioid use disorder: A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial. Lancet 2019;393:778-90.	
Primary Endpoint	• Mean percentage abstinence for participants: ○ **41.3% (39.66%) BUP-XR 300/300; p<0.0001** ○ **42.7% (38.5%) BUP-XR 300/100; p<0.0001** ○ 5.0% (17.0) for placebo
Secondary Endpoints	• Number of patients who were >/= 80% abstinent: ○ 57 (29%) XR 300/300, 55 (28%) XR 300/100, 2 (2%) placebo • Opioid Craving VAS: ○ Number of participants: 192, 191, 96 ○ Least squares mean change from baseline at week 24: ▪ XR 300/300: -0.9 (1.63; -4.1 to 2.3) ▪ XR 300/100: 2.1 (1.63; -1.2 to 5.3) ▪ Placebo: -11.5 (2.48; 6.6 to 16.4) • COWS: ○ Number of participants: 193, 192, 96 ○ Least squares mean change from baseline at week 24: ▪ XR 300/300: -1.1 (0.21; -1.5 to -0.7) ▪ XR 300/100: -0.5 (0.22; -0.9 to 0.4) ▪ Placebo: -0.1 (0.35; -0.8 to 0.6)
Conclusion	• Authors concluded that percentage abstinence was significantly higher in both BUP-XR groups when compared to placebo.

Subjects achieving varying percentages of opioid-free weeks



Haight BR, et al. *Lancet* 2019;393:778-90.

Sublocade® RECOVER Trial

- Environmental and socio-economic factors related to recovery
- 50.8% for all participants had sustained abstinence for 12 months
- Self-reported abstinence:
  - Baseline: 62.7%, 6 months: 70.3%, 12 months: 66.4%
- Relationship of treatment duration with self-reported past week abstinence:

	Baseline (%)	3m (%)	6m (%)	9m (%)	12m (%)
0-2m	38.1	51.1	45.5	50.2	58.6
3-5m	44.8	65.0	64.8	67.3	48.8
6-11m	63.9	74.7	76.3	68.0	70.8
12m	80.4	87.1	83.9	80.5	82.1

Ling W, et al. *American Society of Addiction Medicine 2019 Annual Conference*. Orlando, FL.

Sublocade® Tolerability

Retention rates

- De novo
  - After 6 months of open label treatment: 65.5%
  - After 12 months of open label treatment: 50.5%
- Rollover
  - 6 months vs. 12 months in rollover 300/300: 66.3% vs. 47.1%
  - 6 months vs 12 months in rollover 300/100: 66.0% vs. 53.9%
- 6 months in rollover placebo: 36.4%

Satisfaction

- 85-90% of participants were satisfied with treatment
- Satisfaction score of somewhat, very, or extremely satisfied: significantly higher for both BUP-XR 300/300 mg and 300/100 mg compared to placebo (87.7% vs. 88.1% vs. 46.2%, $p<0.001$)

Ling W, et al. *J Addict Med* 2019;13:442-9.
Andorn AC, et al. *J Clin Psychopharmacol* 2020;40:231-9.

Sublocade® Safety

- Serious TEAEs occurred more frequently in the BUP-XR 300/300 group (n=5, 4.4%)
- Severe TEAEs occurred more frequently in the de novo group (n=36, 8.7%)
- TEAEs leading to discontinuation were more frequent in the de novo group (n-14, 3.4%)
- Most common TEAEs leading to discontinuation:
  - Constipation, injection-site pain, nausea, headache, insomnia, nasopharyngitis, and injection-site erythema
- 46 (6.9%) participants had a dose reduction due to a TEAE,
- Most common TEAEs leading to dose reduction:
  - Lethargy/somnolence (1.9%) and increased LFTs (1.5%)

TEAEs= Treatment emergent adverse events

Andorn AC, et al. *J Clin Psychopharmacol* 2020;40:231-9.

Sublocade® Toxicity- From Trials

System Organ Class	Placebo, count (%)	Buprenorphine XR 300/100 mg, count (%)	Buprenorphine XR 300/300 mg, count (%)
Total	**100**	**203**	**201**
Gastrointestinal disorders	**12 (12)**	**51 (25.1)**	**45 (22.4)**
General disorders and administration site conditions	**17 (17)**	**40 (19.7)**	**49 (24.4)**
Investigations	**2 (2)**	**21 (10.3)**	**19 (9.5)**
Increased ALT	0	2 (1)	10 (5)
Increased AST	0	7 (3.4)	9 (4.5)
Increased blood CPK	1 (1)	11 (5.4)	5 (2.5)
Increased GGT	1 (1)	6 (3)	8 (4)
Nervous system disorders	**7 (7)**	**35 (17.2)**	**25 (12.4)**

- Total with an injection site reaction: 140/848 (16.5%)

Sublocade [package insert]. North Chesterfield, VA: Indivior, Inc; 2017.

Long-Term Safety of Sublocade®

- De novo group: receive monthly injections for up to 12 months
- Rollover group: will receive a monthly injection for up to 6 months
- 669 participants entered study with 406 (60.7%) completed it
  - 412 de novo
  - 113 rollover BUP-XR 300/300
  - 112 rollover BUP-XR 300/100
  - 32 rollover placebo
- TEAEs expereinced:
  - 73.8% in the de novo group experienced a TEAE during the 12 month period
  - 58.0% in the rollover BUP-XR 300/300
  - 53.1% in the rollover BUP-XR 300/100

TEAEs= Treatment emergent adverse events

Andorn AC, et al. *J Clin Psychopharmacol* 2020;40:231-9

Long-Term Safety of Sublocade®

- Serious TEAEs occurred more frequently in the BUP-XR 300/300 group (n=5, 4.4%)
- Severe TEAEs occurred more frequently in the de novo group (n=36, 8.7%)
- Mean (SD) number of doses among the 520 participants with at least 1 TEAE was 9.7 (3.6)
- 46 (6.9%) participants had a dose reduction due to a TEAE
  - Most common TEAEs related to this being lethargy/somnolence (1.9%) and increased liver function tests (1.5%)
  - 30 of these participants continued the 100 mg dose

TEAEs= Treatment emergent adverse events

Andorn AC, et al. *J Clin Psychopharmacol* 2020;40:231-9

Brixadi™ Efficacy

Objective

- To evaluate the efficacy of subcutaneous (SC) buprenorphine vs. SL buprenorphine-naloxone (BUP-NX) for OUD

Design

- 24 week, double-blind, double-dummy, active-controlled, multisite, phase 3 randomized trial

Methods

- Patients received the assigned active agent plus a matched placebo
- First week targeted 16 mg SL BUP-NX by day 2 and 24 mg weekly of SC BUP by day 4
- Dosages after day 4 were flexible
- Weekly visits from weeks 1 to 11 with 7 day SL supplies, then monthly visits from weeks 12 to 24 with monthly SL supplies

Lofwall MR, et al. *JAMA Intern Med* 2018; 178:764-73.

Brixadi™ Efficacy- Results

Endpoints

- Mean percentage of negative urine samples

Patient Population

- 428 patients: 213 SC BUP, 215 SL BUP-NX

Results

- 69.0% in the SC-BUP and 72.6% in the SL BUP-NX completed the study
- Opioid-negative urine samples found to be noninferior when comparing the two groups (6.7 [-0.1-13.6]), $p<0.001$
- % responders found to be noninferior (3.0 [-4.0 to 9.9]), $p<0.001$

Lofwall MR, et al. JAMA Intern Med 2018; 178:764-73.

Brixadi™ Toxicity

- In the previous study, 21 had at least one severe adverse event
  - 2 were possibly related to the study drug, which happened in the SL BUP-NX group
- Number with at least one:
  - 119 (55.3%) in SL BUP-NX and 128 (60.1%) in SC BUP
- Most common adverse event (for both groups)
  - Injection-site pain, headache, constipation, nausea (all occurred in <10%)

Lofwall MR, et al. *JAMA Intern Med* 2018; 178:764-73.

Long-Term Safety of Brixadi™

- Long-term study of both weekly and monthly injections over 48 weeks
- 228 participants enrolled with 227 receiving at least one injection
  - 33.9% treated with weekly injection
  - 33.9% treated with monthly injection
- 143 of 227 (63%) of participants experienced one TEAE, and 26.4% had one adverse effect related to the study medication
- Most common TEAEs (≥5%):
  - Injection site pain (pain, swelling, erythema)
  - Nasopharyngitis
  - Nausea
  - UTI
  - Vomiting
- Higher incidence of TEAEs in participants converted from SL buprenorphine product to injection (68.9%) than new-to-treatment participants (32.4%)

TEAEs= Treatment emergent adverse events

Frost M, et al. Addiction 2019; 114:1416-26.

Long-Term Retention and Efficacy with Brixadi™

- 118 of 227 (82.8%) of participants completed 24 weeks of treatment
- 167 of 227 (73.6%) of participants completed 48 weeks of treatment (full study period)
- Mean (SD) and median duration of treatment was 39.1 weeks (16.2) and 48 weeks
- New to treatment participants:
  - Percentage of participants with opioid-negative urine samples and self-reports (composite): 63% (17 out of 22)
- Converted from SL buprenorphine participants:
  - Percentage negative for opioid-negative urine samples and self-reports (composite): 82.8% (111 out of 134) [vs. 78.4% at day 1]

Frost M, et al. Addiction 2019; 114:1416-26.

Long-Term Retention and Efficacy with Brixadi™

- Reported Experience:
  - 162 (71.4%) of 227 completed survey regarding important characteristics of buprenorphine treatment and satisfaction with study drug vs. SL buprenorphine
    - 29 new to treatment and 133 converted from SL
  - 91 (68.4%) out of 133 reported that study drug was “much better” than thair previous treatment with SL buprenorphine
  - Top 3 reported characteristics that were important for a buprenorphine treatment:
    - Does not require daily medication, allowed to travel with no medication, spares regular trip to pharmacy

Frost M, et al. Addiction 2019; 114:1416-26.

Place in Therapy

Potential Patients Who May Benefit

- Unwanted disruptions in treatment
- Difficulty with daily adherence
- Concern for safe storage
- At risk for diversion or misuse of a product in their possession

Lofwall MR, et al. *JAMA Intern Med* 2018; 178:764-73.

Conclusion

Pros of Sublocade®	Cons of Sublocade®	Future thoughts
• No daily doses • Reduce stigma • Assist in difficult clinical situations • Effective with limited adverse effects • Patient assistance programs available	• Process must be in place for REMs • Must be refrigerated • Must be on transmucosal buprenorphine product for 7 days • Only to be administered by healthcare professional • Dose adjustments • Must ensure patient is appropriate for a monthly injectable • Coverage	• How long to continue therapy • Will patients prefer weekly or monthly dosing • Sublocade® vs. Brixadi™

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