# Calcium, magnesium, potassium, and sodium oxybates (XYWAV™) National Drug Monograph January 2021

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.*

## FDA Approval Information[1]

### Description/Mechanism of Action

- The mechanism of action of oxybate salts, referred here on in as lower-sodium oxybate (LXB), to treat narcolepsy with cataplexy is unknown; however, its efficacy is likely to be mediated through its actions of $GABA_B$ on noradrenergic, dopaminergic, and thalamocortical neurons during sleep.

### Indication(s) Under Review in This Document

- Treatment of cataplexy or excessive daytime sleepiness (EDS) in patients ≥7 years of age with narcolepsy, and for the treatment of idiopathic hypersomnia (IH) in adults.
- **Dosage Form(s) Under Review**
- Oral solution: 0.5 g/mL in 180 mL bottle (no specific flavoring added)

### REMS

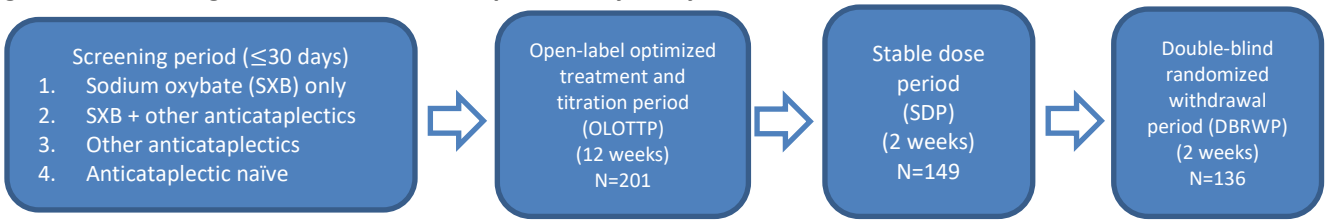
- Refer to XYWAV™ and XYREM® REMS program. Refer to Special Handling Drugs on the PBM website for

## Clinical Evidence Summary[1-2]

### Efficacy Considerations:

- The safety and efficacy of LXB was established in a phase III double-blind, placebo-controlled, randomized withdrawal multicenter study involving 201 adult patients with primary diagnosis of narcolepsy with cataplexy, based on the diagnostic criteria from the *International Classification of Sleep Disorders,* 3rd edition or *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition.
- The trial design is detailed in **Figure 1**. Following the SDP period, 71 patients participated in an optional 24-week open-label extension (OLE) safety period (not depicted in Figure 1; data not available).

**Figure 1: Trial Design and Treatment Groups at Study Entry**




- The **primary outcome** was the change in weekly number of cataplexy attacks from during the two-week SDP to during the two-week DBRWP.
- The key **secondary outcome** was change in the Epworth Sleepiness Scale (ESS) score from the end of SDP to the end of DBRWP.
- Enrollment criteria included history of ≥14 cataplexy attacks per typical two-week period prior to receiving any narcolepsy treatment.
- Patient characteristics in safety population (n=201):

- Age (mean): 37.2 years (18-70); Sex (female): 60.7%; Race (white): 88.1%
- Disrupted nightmare sleep (63%); sleep-related hallucinations (60%); and sleep paralysis (60%); hypertension (17.4%); diabetes mellitus (3%); obesity (7.0%).
- At study entry, the median (minimum, maximum) dose of SXB was 7.5 (4.5, 9.0) g/night.
- Overall, 60% of patients (n=121) were taking other medications for treatment of narcolepsy symptoms including amphetamines (~11%), methylphenidates (~13%), modafinil/armodafinil (~29%); or a combination of these agents (7%).
- Other anticataplectics included (in order from most common to least common): selective serotonin-norepinephrine reuptake inhibitors (SSNRIs)/selective norepinephrine reuptake inhibitors (SNRIs); tricyclic antidepressants (TCAs); selective serotonin reuptake inhibitors (SSRIs); pitolisant; and other antidepressants.

- All patients taking SXB were transitioned gram per gram to the same dose of LXB and increased at the investigator's discretion to a maximum of 9.0 gram/night, if required.
- Patients naïve to SXB were initiated on LXB 4.5 gram/night, given as one 2.5-gram dose, followed by another 2-gram dose 2-4 hours later to a maximum of 9.0 gram/night.
- Efficacy Outcomes **(Refer to Table 1)**: LXB significantly reduced the weekly cataplexy scores, 95% CI [-6.04, -1.50] and ESS scores, 95% CI [-4.0, -1.0] compared to placebo.
- Post-hoc analysis: During DBRWP, the median number of cataplexy-free days per week was 3.5 in weeks 1 and 2 in the placebo groups compared to 5 and 5.6 days for patients randomized to LXB during week 1 and 2, respectively. At study entry, patients taking SXB reported 5-6 days of cataplexy-free days per week.
- Most patients randomized to the LXB group reported better patient global impression of change (PGIc) ratings, SF-36 physical component summary scores, and SF-36 mental component summary scores.
- The percentage of patients taking stimulants and/or wake-promoting agents (WPA) remained the same throughout the entire study. Doses of stimulants/WPAs remained generally the same except an amphetamine dose was decreased in week 7 for one patient; and methylphenidate was replaced with amphetamine at week 14 in another patient.

**Table 1: Lower Sodium Oxybate (LXB) Efficacy Results**

| Efficacy Measures | PLC (n=65) Mean (SD) | LXB (n=69) Mean (SD) |
|---|---|---|
| **Average Weekly Number of Cataplexy Attacks** | | |
| Baseline (2 weeks of the SDP) | 7.2 (14.4) | 8.9 (16.8) |
| Change from baseline to 2 weeks of the DBRWP | 11.5 (24.8) | 0.1 (5.8) |
| **Epworth Sleepiness Score** | | |
| Baseline (2 weeks of the SDP) | 12.6 (5.5) | 13.6 (5.3) |
| Change from baseline to 2 weeks of the DBRWP | 3.0 (4.7) | 0.0 (2.9) |

## Safety Considerations:

- One or more treatment emergent adverse events (TEAEs) was reported by 76% of the study population including headache (20%), nausea (13%), dizziness (10%), and worsening of cataplexy (10%). Due to the trial design, adverse events reported may not be exclusively related to the administration of LXB since anticataplectics were tapered and stopped during the OLOTTP. However, TEAEs were reported more commonly in both the other anticataplectics and anticataplectic naïve groups, suggesting that the tolerability of LXB is similar to that of SXB.[4-5]
- In the DBWRP safety population, one or more TEAEs occurred in 34% and 19% of patients taking placebo and LBX, respectively.
- **Serious Adverse Events / Deaths / Discontinuation**
  - Fifty-two patients (26%) discontinued treatment prior to reaching the SDP. Nineteen (36.5%) discontinuations were due to adverse events, with the most common being cataplexy.

## Other Considerations[1-3,6]

- **Boxed warnings:**
  - **Central nervous system (CNS) depression:** LXB is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with LXB at recommended doses.
  - **Abuse and misuse:** The active moiety of LXB is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death.
- **Contraindications:**
  - Concomitant use with sedative-hypnotic agents or alcohol
  - Succinic semialdehyde dehydrogenase deficiency
- **Other warnings/precautions**:
  - **CNS depression:** Respiratory depression and obtundation have occurred in patients taking LXB at recommended doses. The use of CNS depressants with LXB may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. Empiric dose reduction or discontinuation of other CNS depressants is recommended if used in combination with LXB is required. If short-term use of an opioid is necessary, interruption of LXB treatment should be considered.
  - **Abuse and misuse:** LXB is a schedule III controlled substance. The active moiety is gamma-hydroxybutyrate (GHB) and is a schedule I controlled substance. Abuse may lead to adverse CNS effects, including seizure, respiratory depression, decreased consciousness, coma, and death.
  - **Respiratory depression and sleep-disordered breathing:** LXB may impair respiratory drive. Increased apneas and desaturation events have been reported with LXB administration, occurring most frequently in those with sleep-related breathing disorders, commonly identified in obese patients, men, postmenopausal women not on hormone replacement therapy, and patients with narcolepsy.
  - **Depression and suicidality:** Patients with a history of depression or suicidality should be monitored closely while taking LXB.
  - **Other behavioral or psychiatric adverse reactions:** Patients should be monitored closely while taking LXB.
  - **Parasomnias including s**leepwalking episodes can occur and should be thoroughly evaluated.
- **Drug interactions:** Similar to sodium oxybate (Xyrem™), a drug-drug interaction exists between divalproex sodium and LXB, increasing systemic exposure of GHB. Therefore, it is recommended to empirically reduce the dose of LXB by at least 20% when used in combination with divalproex sodium.

## Other Considerations[1-3,6]

- **Pharmacokinetics** are largely similar to that of SXB. However, in the fasted state, LXB has a lower $C_{max}$ when compared to SXB. In phase I studies, this lower $C_{max}$ was associated with lower incidences of nausea and vomiting.[7]
- **Special populations**
  - **Pregnancy:** No data regarding the utilization of LXB or SXB in pregnant women. In pregnant rats and rabbits, the administration of up to 1000 mg/kg/day produced no clear evidence of developmental toxicity; however, increased stillbirths and decreased offspring postnatal viability and growth were observed.
  - **Breastfeeding:** GHB is excreted in human milk. There is insufficient data regarding the administration to breastfed infants and milk production in nursing mothers.
- **Storage/administration**
  - Store at room temperature.
  - Each dose should be diluted with ¼ cup of water in provided empty pharmacy containers.
  - Diluted solution should be used within 24 hours.

- Dose should be administered at bedtime, on an empty stomach, at least two hours after eating, while patient is lying down in bed. The second dose should be administered 2.5-4 hours after the first, in the same manner.

## Other Therapeutic Options[1,3-6,8-12]

Alternative treatments for cataplexy and EDS in narcolepsy are listed in **Table 2** below, though no head-to-head studies between any of the agents exist.

**Table 2: FDA Treatment Alternatives for Cataplexy and EDS in Narcolepsy**

| Drug | Formulary Status | FDA-Approved Indications | Other Considerations |
|---|---|---|---|
| Calcium, magnesium, potassium, sodium oxybates (Xywav™) | TBD | Treatment of cataplexy or EDS in narcolepsy in those ≥7 years of age | • Must use the diluted solution within 24 hours<br>• REMS program<br>• CNS depression, abuse and misuse, and restricted access<br>• Na content: 6-9 gram dose = 87-131 mg sodium<br>• In the fasted state, LXB has a lower Cmax than SXB, which was associated with less nausea and vomiting in phase I clinical trials. Clinical significance unknown.<br>• Schedule III controlled substance |
| sodium oxybate (Xyrem®) | PA-F | Same as Xywav™ | • Same as XYWAV™ except higher Na content<br>• Na content: 6-9 gram dose = 1,100 -1640 mg sodium |
| pitolisant (Wakix™) | Non-Formulary with criteria | Treatment of cataplexy or EDS in adults with narcolepsy | • FDA approved for the treatment of EDS or cataplexy<br>• No evidence of abuse, tolerance, rebound or withdrawal<br>• Long term safety and efficacy -unclear<br>• Avoid with other drugs known to prolong QT interval and centrally acting H1 receptor antagonists<br>• Not a scheduled controlled substance |
| CNS stimulants (amphetamines, methylphenidates) | Dependent on drug | Treatment of narcolepsy, daytime sleepiness | • Boxed warning due to high potential for abuse, drug dependence, and misuse may cause sudden death and serious CV adverse events<br>• Potential for serious psychological AEs in pts with preexisting psych disorders<br>• Lowers seizure threshold<br>• Schedule II controlled substances |
| solriamfetol (Sunosi™) | Non-formulary with criteria | Improve wakefulness in adults with EDS associated with narcolepsy or OSA | • Increase in BP and heart rate and psychiatric symptoms (dose dependent)<br>• Long-term safety and efficacy-unclear<br>• Schedule IV controlled substance |
| modafinil (Provigil™) and armodafinil (Nuvigil™) | Formulary | Improve wakefulness in adults with EDS associated with narcolepsy, OSA, or shift work disorder | • Potential teratogenicity including congenital cardiac anomalies<br>• Substrates, inducers and inhibitors of CYP450 isoenzymes<br>• Labeled warnings for Stevens-Johnson Syndrome, angioedema, anaphylactoid reactions, and multi-organ hypersensitivity reactions<br>• Schedule IV controlled substance |

## Projected Place in Therapy

- Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, hallucinations, and sleep paralysis.[13] Prevalence of narcolepsy is ~ 1 in every 2000 individuals. For FY 19, using ICD code G47.4 for narcolepsy, it is estimated that 6,367 Veterans have narcolepsy in the VA.[14]
- Narcolepsy Type 1 (NT1) which includes cataplexy, is the most common type, affecting approximately 25-50 people per 100,000 people.[15]

- Clinical safety and efficacy outcomes are based on a phase 3 trial, 16 weeks in duration with two weeks of data comparing lower-sodium oxybate (LXB) vs placebo. Six individuals included in study were ≥ 65 years of age.
- Sodium oxybate (SXB) is recommended for the treatment of cataplexy in several Clinical Practice Guidelines based on Class 1 evidence.[16-17] Lower-sodium oxybate (LBX) is also effective in treating cataplexy. No head to head trials are available comparing LXB and SXB or LBX to any other agents indicated for narcolepsy.
- It appears most patients can be effectively transitioned from SXB to LXB without any difficulties. Side effect profiles are similar between SXB and LBX. Like SBX, LBX would likely be used in combination with other therapies in order to adequately control all symptoms of narcolepsy.
- The American Heart Association recommends limiting sodium intake to 2,300 mg per day, with an even more strict limit of 1,500 mg per day for most adults, especially those with high blood pressure.[18] Since LBX has 92% lower sodium content compared to SXB, it offers another treatment option for treating cataplexy in patients with NT1 and cardiovascular/renal disease or other health condition/valid medical reason requiring a lower daily sodium consumption.

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