

PRIOR AUTHORIZATION POLICY

POLICY: Xyrem® (sodium oxybate oral solution – Jazz Pharmaceuticals)

TAC APPROVAL DATE: 03/20/2019

OVERVIEW

Xyrem is a central nervous system (CNS) depressant indicated for the treatment of cataplexy in narcolepsy and for the treatment of excessive daytime sleepiness (EDS) in narcolepsy in patients ≥ 7 years of age.¹ The mechanism of action of Xyrem in the treatment of narcolepsy is unknown. It is hypothesized that the therapeutic effects of Xyrem on cataplexy and excessive daytime sleepiness are mediated through GABA_B actions at noradrenergic and dopaminergic neurons and also at thalamocortical neurons.

Guidelines recommend the use of Xyrem for the treatment of narcolepsy and for cataplexy due to narcolepsy.²⁻³ The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (2007) list Xyrem as effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (*Standard*) and modafinil as an effective for treatment of daytime sleepiness due to narcolepsy (*Standard*). Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are considered effective for the treatment of daytime sleepiness due to narcolepsy (*Guideline*). Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and venlafaxine may be effective for the treatment of cataplexy (*Guideline*). Selegiline may be an effective treatment for cataplexy and daytime sleepiness (*Option*). *Standard* recommendations are considered to be generally accepted patient-care strategies that reflect a high degree of clinical certainty based on Level I evidence or overwhelming Level II evidence. *Guideline* recommendations are considered to be patient-care strategies that reflect a moderate degree of clinical certainty based on Level II evidence or a consensus of Level III evidence. *Option* recommendations are considered to be patient-care strategies that reflect uncertain clinical use based on inconclusive or conflicting evidence or conflicting expert opinion. At the time this practice parameter was written, published studies involving Nuvigil® (armodafinil tablets) were limited.

Xyrem is the sodium salt of gamma hydroxybutyrate (GHB) and is a Schedule III controlled substance.¹ Abuse of GHB (a Schedule I controlled substance), 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. Because of the risks of CNS depression, abuse, and misuse, Xyrem is available only through a restricted distribution program called the Xyrem Success Program, using a centralized pharmacy. Healthcare professionals who prescribe Xyrem and patients must enroll in the Xyrem Success Program and must comply with the requirements to ensure the drug's safe use.

In 2012, the Food and Drug Administration (FDA) issued a safety communication for Xyrem, reminding healthcare professionals and patients that the combined use of Xyrem with alcohol or CNS depressant drugs can markedly impair consciousness and may lead to severe respiratory depression.⁴ At that time, the use of alcohol with Xyrem was a new contraindication added to the Xyrem label, which already contraindicated its use with insomnia medications. The use of Xyrem with other CNS depressant drugs (such as opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, and muscle relaxants) should generally be avoided.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xyrem. Xyrem has been associated with significant risks, including CNS and respiratory depression, and it also has the potential for abuse, misuse, and overdose. All approvals are provided for the duration noted below.

Automation: Grandfathering is not clinically necessary for Xyrem. Refer to the AUM reference guide for additional information.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xyrem is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Cataplexy Treatment in Patients with Narcolepsy.** Approve for 1 year if the patient meets the following criteria (**A, B, and C**):
 - A) The patient has tried one of the following treatments: a tricyclic antidepressant (TCA) [e.g., amitriptyline, desipramine, imipramine], a selective serotonin reuptake inhibitor (SSRI) [e.g., fluoxetine, sertraline, paroxetine], or venlafaxine; AND
 - B) Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT); AND
 - C) Xyrem has been prescribed by a sleep specialist physician or a neurologist.

Xyrem is indicated for the treatment of cataplexy in narcolepsy.¹ AASM practice parameters for the treatment of narcolepsy and other hypersomnias of central origin list Xyrem as effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (*Standard*) and modafinil as an effective for treatment of daytime sleepiness due to narcolepsy (*Standard*).² TCAs, SSRIs, and venlafaxine may be effective for the treatment of cataplexy (*Guideline*).

2. **Excessive Daytime Sleepiness (EDS) in Patients with Narcolepsy.** Approve for 1 year if the patient meets the following criteria (**A, B, and C**):
 - A) The patient has tried two central nervous system (CNS) stimulants (e.g., methylphenidate, dextmethylphenidate, dextroamphetamine), modafinil, or armodafinil; AND
 - B) Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT); AND
 - C) Xyrem has been prescribed by a sleep specialist physician or a neurologist.

Xyrem is indicated for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.¹ AASM practice parameters for the treatment of narcolepsy and other hypersomnias of central origin list Xyrem as effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (*Standard*) and modafinil as an effective for treatment of daytime sleepiness due to narcolepsy (*Standard*).² Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are considered effective for the treatment of daytime sleepiness due to narcolepsy (*Guideline*).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xyrem has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Fibromyalgia.** The effectiveness of Xyrem in fibromyalgia has been evaluated in clinical trials of varying size.⁵⁻¹⁰ However, due to safety concerns, Xyrem is not recommended for approval for fibromyalgia at this time. Duloxetine, Lyrica® (pregabalin capsules and oral solution), and Savella® (milnacipran tablets) are indicated for the treatment of fibromyalgia.¹¹⁻¹³ Other recommended treatments include TCAs (i.e., amitriptyline), cyclobenzaprine, gabapentin, and SSRIs (i.e., fluoxetine, sertraline, paroxetine).¹⁴

The European League Against Rheumatism (EULAR) has issued updated evidence-based recommendations for the management of fibromyalgia (2016) stating that initial management should involve patient education and focus on nonpharmacological therapies.¹⁵ In case of non-response, further therapies should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation program (for severe disability). EULAR notes that the European Medicines Agency and the FDA refused approval of Xyrem for fibromyalgia because of safety concerns. EULAR's position on Xyrem for fibromyalgia is strongly against with 94% agreement.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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2. Morgenthaler TI, Kapur VK, Brown TM, et al. Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin: An American Academy of Sleep Medicine Report. Available at: http://www.aasmnet.org/Resources/PracticeParameters/PP_Narcolepsy.pdf. Accessed on March 14, 2019.
3. Wise MS, Arand DL, Auger R, et al. Treatment of narcolepsy and other hypersomnias of central origin: An American Academy of Sleep Medicine Review. *Sleep*. 2007;30(12):1712-27. Available at: http://www.aasmnet.org/Resources/PracticeParameters/Review_Narcolepsy.pdf. Accessed on March 14, 2019.
4. Food and Drug Administration (FDA) drug safety communication: warning against the use of Xyrem (sodium oxybate) with alcohol or drugs causing respiratory depression. Page last updated: 1/19/2016. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm332029.htm>. Accessed on March 14, 2019.
5. Spaeth M, Bennett RM, Benson BA, et al. Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: results of an international phase 3 trial. *Ann Rheum Dis*. 2012;71:935-942.
6. Russel IJ, et al. Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: results from a 14-week, randomized, double-blind, placebo-controlled study. *Pain*. 2011;152(5):1007-17.
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11. Lyrica® (prescribing information). New York, NY: Pfizer Inc.; May 2018.
12. Cymbalta® (prescribing information). Indianapolis, IN: Lilly USA, LLC; December 2017.
13. Savella® tablets (prescribing information). St. Louis, MO: Forest Pharmaceuticals, Inc.; November 2017.
14. Clauw DJ. Fibromyalgia: a clinical review. *JAMA*. 2014;311(15):1547-1555.
15. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017;76(2):318-328.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	2/3/2016

DEU revision	7/16/16: Updated the Automation section to include a reference to the AUM reference guide for information on non-clinical requirements for the Xyrem prior authorization.	NA
Annual revision	No change to criteria.	03/01/2017
Annual revision	No change to criteria.	03/07/2018
Selected revision	Change to criteria for Cataplexy Treatment in Patients with Narcolepsy: removed modafinil and Nuvigil from list of previous treatment options. Added requirement of sleep studies (polysomnography and a MSLT) to both approval conditions. Changed the required number of previous alternative CNS stimulants (e.g., methylphenidate, dexamethylphenidate, dextroamphetamine), modafinil, or armodafinil from one to two for the criterion for Excessive daytime sleepiness in patients with narcolepsy.	07/25/2018
Annual revision	No change to criteria.	03/20/2019

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; * For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; NA – Not applicable; MSLT – Multiple sleep latency test; CNS – Central nervous system.