MEDICAL MUTUAL®

Drug Policy

Policy:	**Wakix (pitolisant)** **Xyrem (sodium oxybate)** **Xywav (calcium, magnesium, potassium, and sodium oxybates)** **Lumryz (sodium oxybate extended release)**	**Annual Review Date: 12/21/2023** **Last Revised Date: 12/21/2023**

OVERVIEW

Wakix is a histamine-3 (H3) receptor antagonist/inverse agonist indicated for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy. Wakix is contraindicated in patients with severe hepatic impairment and can cause QT interval prolongation and should be avoided in patients who have risk factors for prolonged QT interval, or who take medications that also increase the QT interval.

Hormonal contraceptives have shown a decrease in efficacy when used with Wakix. Patients using hormonal contraception are advised to use an alternative, non-hormonal contraceptive when taking during the same period as Wakix as well as for 21 days following discontinuation of therapy. Wakix use with centrally acting histamine-1 receptor antagonists is not recommended as Wakix increases the levels of histamine in the brain and the effect of Wakix may be reduced by H1 receptor antagonists that cross the blood-brain barrier (e.g. diphenhydramine, TCA's, Mirtazapine etc.) Other drug interactions of note: using Wakix with strong CYP2D6 inhibitors or strong CYP3A4 inducers could impact the exposure of pitolisant and therefore may require a dosage adjustment in the Wakix.

Xyrem, Lumryz (sodium oxybate) and Xywav (calcium, magnesium, potassium and sodium oxybates) are central nervous system depressants that reduce excessive daytime sleepiness (EDS)and cataplexy in patients with narcolepsy, 7 years of age and older. Xyrem and Xywav are intended for oral administration. A successor to Xyrem, Xywav has 92% less sodium (approximately 1,000mg and 1,500mg less per night) than Xyrem. For patients transitioning from Xyrem, the starting dose of Xywav is the same as the Xyrem dose.The active moiety of Xyrem and Xywav is oxybate or gamma-hydroxybutyrate (GHB). Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Xyrem and Xywav are subject to the Xywav and Xyrem REMS program that requires prescribers and dispensers to be trained and certified. Patients must be enrolled in the REMS program before they receive Xywav or Xyrem.

POLICY STATEMENT

This policy involves the use of Wakix, Xyrem, Lumryz and Xywav. Prior authorization is recommended for pharmacy benefit coverage of Wakix, Xyrem, Lumryz and Xywav. Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval** for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Wakix, Xyrem and Xywav, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Wakix, Xyrem and Xywav be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy [documentation required].

RECOMMENDED AUTHORIZATION CRITERIA

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

1. Excessive Daytime Sleepiness (EDS) With Narcolepsy

Criteria. *Patient must meet the following criteria*

- **A.** Patient is 18 years of age or older. AND
- **B.** Patient must meet one of the following criteria (a OR b):
  - a. There are no conditions contributing to or worsening symptoms of narcolepsy; OR
  - b. Other conditions contributing to or worsening excessive daytime sleepiness have been addressed and treated; AND
- **C.** The patient has been diagnosed with Excessive Daytime Sleepiness (EDS) with narcolepsy; AND
- **D.** Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT); AND
- **E.** Must be prescribed by or in consultation with a sleep disorder specialist, pulmonologist, psychiatrist, or neurologist; AND
- **F.** Patient must have trialed generic armodafinil OR modafinil unless the patient has a contraindication or is intolerant to the use of armodafinil or modafinil.

Initial Approval/ Extended Approval.

A) *Initial Approval: 1 year*

B) *Extended Approval: 1 year*

2. Cataplexy with Narcolepsy

Criteria. *Patient must meet the following criteria*

- **A.** Patient is 18 years of age or older. AND
- **B.** Patient must meet one of the following criteria (a OR b):
  - a. There are no conditions contributing to or worsening symptoms of narcolepsy; OR
  - b. Other conditions contributing to or worsening cataplexy have been addressed and treated; AND
- **C.** The patient has been diagnosed with cataplexy with narcolepsy; AND
- **D.** Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT); AND
- **E.** Must be prescribed by or in consultation with a sleep disorder specialist, pulmonologist, psychiatrist, or neurologist;
- **F.** Patient meets ONE of the following criteria (i or ii);
  - a. Patient has tried dextroamphetamine; OR
  - b. Patient has a contraindication or intolerance to dextroamphetamine, according to the prescriber.

Note: Contraindications to dextroamphetamine include a history of substance use disorder; advanced arteriosclerosis, symptomatic cardiovascular disease, and/or moderate to severe hypertension; hyperthyroidism; known hypersensitivity to sympathomimetic amines; glaucoma; agitated states; and concomitant administration with monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs.

Initial Approval/ Extended Approval.
A) *Initial Approval: 1 year*
B) *Extended Approval: 1 year*

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

3. Excessive Daytime Sleepiness (EDS) With Narcolepsy
Criteria. *Patient must meet the following criteria*

- **A.** Patient is 7 years or older; AND
- **B.** Patient does not have succinic semialdehyde dehydrogenase deficiency; AND
- **C.** The patient is not taking CNS depressant concomitantly (e.g. ethanol, sedative hypnotics, anxiolytics, barbiturates, benzodiazepines); AND
- **D.** Patient has tried two of the following treatments: a central nervous system (CNS) stimulant, modafinil or armodafinil; Note: examples of CNS stimulants are methylphenidate, dexmethylphenidate, and dextroamphetamine; AND
- **E.** If patient is 18 years or older, both of the following (a and b) must be met;
  - a. Patient has tried Sunosi or has a contraindication to Sunosi; AND
  - b. Patient has tried Wakix or has a contraindication to Wakix; AND
- **F.** Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT) [documentation required]; AND
- **G.** Xyrem/Xywav has been prescribed by a sleep disorder specialist, pulmonologist, psychiatrist, or neurologist.

Initial Approval/ Extended Approval.
A) *Initial Approval: 1 year*
B) *Extended Approval: 1 year*

4. Cataplexy with Narcolepsy
Criteria. *Patient must meet the following criteria*

- **A.** Patient is 7 years of age or older; AND
- **B.** The patient is not taking a CNS depressant concomitantly (e.g. ethanol, sedative hypnotics, anxiolytics, barbiturates, benzodiazepines); AND
- **C.** The patient does not have succinic semialdehyde dehydrogenase deficiency; AND
- **D.** If patient is 18 years or older, the patient has tried Wakix or has a contraindication to Wakix; AND
- **E.** Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT) [documentation required]; AND
- **F.** Xyrem/Xywav has been prescribed by a sleep disorder specialist, pulmonologist, psychiatrist, or neurologist.

G. Patient meets ONE of the following criteria (i or ii);
   a. Patient has tried dextroamphetamine; OR
   b. Patient has a contraindication or intolerance to dextroamphetamine, according to the prescriber.

   Note: Contraindications to dextroamphetamine include a history of substance use disorder; advanced arteriosclerosis, symptomatic cardiovascular disease, and/or moderate to severe hypertension; hyperthyroidism; known hypersensitivity to sympathomimetic amines; glaucoma; agitated states; and concomitant administration with monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs.

Initial Approval/ Extended Approval.
A) *Initial Approval: 1 year*
B) *Extended Approval: 1 year*

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5. Idiopathic Hypersomnia (Xywav only)
Criteria. *Patient must meet the following criteria*

A. Patient is 18 years of age or older; AND
B. The patient has tried or has a contraindication to modafinil; AND
C. The patient has been evaluated using polysomnography [documentation required]; AND
D. The patient has been evaluated using MSLT [documentation required]; AND
E. Must be prescribed by or in consultation with a sleep disorder specialist, pulmonologist, psychiatrist, or neurologist; AND

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Wakix, Xyrem and Xywav have 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Long-Term Maintenance of Fibromyalgia (Xyrem, Lumryz and Xywav).** An FDA advisory panel overwhelmingly rejected the application for approval of Xyrem for the treatment of fibromyalgia on August 20, 2010. This decision was based on conclusions that clinical trials brought forward lacked significant efficacy compared to current fibromyalgia medications on the market. Also, the lack of information detailing drug interactions within the study samples were concerning.

2. **Concomitant use of Xyrem (sodium oxybate oral solution), Lumryz, Xywav (calcium, magnesium, potassium, and sodium oxybates oral solution), and/or Wakix (pitolisant tablets) with Xyrem, Lumryz, Xywav or Wakix.** Xyrem (sodium oxybate oral solution) and Xywav have the same active ingredient (oxybate, a central nervous system depressant) and have not been studied for use in combination or as alternating treatments. Wakix, an antagonist/inverse

agonist of the histamine-3 receptor, is indicated for excessive daytime sleepiness and cataplexy in adults with narcolepsy. Currently, there are no published studies evaluating combination use of these medications.

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

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational, or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

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